CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214985Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memo

Date:	December 22, 2021
Reviewer:	Dinci Pennap, PhD, MPH, MS Division of Epidemiology I
Team Leader:	Yandong Qiang, MD, PhD, MHS, MPH Division of Epidemiology I
Division Director:	Simone P Pinheiro, ScD MSc Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concern
Drug Name:	Quviviq™ (daridorexant)
Application Type/Number:	NDA 214985
Applicant/sponsor:	Idorsia Pharmaceuticals, Ltd.
OSE RCM #:	2021-1142
PDUFA Date:	January 08, 2022

Reference ID: 4909902

1. BACKGROUND INFORMATION

1.1. Medical Product

Daridorexant (Quviviq™) is a dual orexin receptor antagonist that functions as a central nervous system depressant with a proposed indication of [redacted] (b) (4) adult patients with insomnia. Orexin-producing neurons are located exclusively in the hypothalamus, but project to and excite specific regions in the brain stem and basal forebrain, where ascending neurotransmitter systems promote arousal and wakefulness via excitation of dopaminergic, noradrenergic, cholinergic, and histaminergic systems. Dual orexin receptor antagonists (DORAs) produce sleepiness by antagonizing these arousal systems. Two orally administered DORAs have been approved (suvorexant in 2014 and lemborexant in 2019) by the FDA for treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Daridorexant is designed as film-coated tablets of 25 mg and 50 mg with the highest proposed therapeutic dose of 50 mg taken orally at night 30 minutes before bedtime. While there are no recommended dose adjustments for patients with renal or mild hepatic impairments, the maximum recommended dosage of daridorexant is 25 mg no more than once per night in patients with moderate hepatic impairment (Child-Pugh score 7–9). It is not recommended in patients with severe hepatic impairment (Child-Pugh score ≥ 10). Daridorexant has a terminal half-life of approximately 8 hours and the primary route of elimination is via feces (approximately 57%), followed by urine (approximately 28%). Only traces of parent drug were found in feces and urine.

The efficacy of daridorexant in the treatment of patients with insomnia was assessed in two confirmatory phase 3 randomized controlled studies, ID-078A301 and ID- 078A302, supported by the interim results from one ongoing double-blind phase 3 extension study, ID-078A303, and two phase 2 dose-finding studies, AC-078A201 and AC-078A202. Its safety was evaluated in three placebo-controlled clinical studies (two 3- month confirmatory studies of identical design [Study 1 and Study 2], and a 9-month extension study [Study 3]). Study 1 included the 50 and 25 mg doses of daridorexant, while Study 2 included 25 and 10 mg daridorexant. A total of 1847 subjects (including approximately 40% elderly subjects [> 65 years old]), received daridorexant 50 mg (N= 308); 25 (N= 618); or 10 mg (N= 306) or placebo (N= 615). A total of 490 subjects were treated with daridorexant for at least 6 months and 314 for at least 12 months. The Sponsor conducted additional nonclinical and clinical abuse potential and dependence studies, as well as an analysis of abuse related adverse events.

The most frequently reported adverse reaction (in at least 2% of subjects and with a >1% difference vs placebo) during double-blinded treatment in Study 1 and Study 2 was headache. No evidence of a dose-response relationship for the frequency or severity of adverse reactions was observed and the adverse reaction profile in the elderly was consistent with the profile in younger patients.

1.2. Safety Concern

As part of a New Drug Application, the Division of Psychiatry requested that the Division of Epidemiology assess the sufficiency of the FDA's Active Risk Identification and Analysis (ARIA) for broad-based signal detection studies of daridorexant use for insomnia during pregnancy.

It is well-known that female patients of childbearing potential are at potential risk of inadvertent in-utero exposure to medications, possibly resulting in risk to the fetus.[1] In the United States, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[2] Insomnia occurs significantly more frequently in women than men.[3, 4] While the reasons for this gender-based difference are unclear, insomnia has been associated with hormonal changes that are unique to women, such as those of menopause or the late-luteal phase of the menstrual cycle.[3] Further, women are more likely to suffer from major depression and anxiety disorders, which are also associated with insomnia.[4]

Pregnant women were excluded from clinical trials during the development of daridorexant and no exposed pregnancy cases were reported. Therefore, there are no available data on daridorexant use in pregnant women to evaluate drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of daridorexant to pregnant rats and rabbits during the period of organogenesis did not cause significant fetal toxicity at doses up to 8 and 10 times the maximum recommended human dose (MRHD) of 50 mg, based on AUC. In rabbits, daridorexant caused maternal toxicity of decreased weight gain and food consumption at 10 times the MRHD based on AUC. The no observed adverse effect levels (NOAELs) for maternal toxicity are approximately 8 and 4 times the MRHD, based on AUC in rats and rabbits, respectively. Oral administration of daridorexant to pregnant and lactating rats did not cause significant maternal or developmental toxicity at doses up to 9 times the MRHD, based on AUC.

Overall, there is limited information on the risk of adverse pregnancy and fetal outcomes following exposure in pregnancy.[a]

In the proposed draft product labeling for daridorexant as of December 1, 2021, the Risk Summary in Section 8 states:

> 8 USE IN SPECIFIC POPULATIONS
>
> 8.1 Pregnancy
>
> Pregnancy Exposure Registry
>
> There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Quviviq during pregnancy. Pregnant women exposed to Quviviq and healthcare providers are encouraged to call Idorsia Pharmaceuticals Ltd at 1-833-400-9611.

[a] QUVIVIQ (daridorexant). Draft clinical review dated November 19, 2021. Division of Psychiatry. U.S. Food and Drug Administration

Risk Summary

There are no available data on Quviviq use in pregnant women to evaluate drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of daridorexant to pregnant rats and rabbits during the period of organogenesis did not cause fetal toxicity or malformation at doses up to 8 and 10 times the maximum recommended human dose (MRHD) of 50 mg, respectively, based on AUC. Oral administration of daridorexant to pregnant and lactating rats did not cause any maternal or developmental toxicity at doses up to 9 times the MRHD, based on AUC (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Daridorexant was administered orally to pregnant rats during the period of organogenesis at doses of 30, 100, and 300 mg/kg/day, which are approximately 1, 3, and 8 times the MRHD of 50 mg, respectively, based on AUC. Daridorexant did not cause any maternal or embryofetal toxicities or fetal malformation at doses up to 300 mg/kg/day. The NOAEL for maternal and fetal toxicity is 300 mg/kg/day, which is approximately 8 times the MRHD of 50 mg, based on AUC.

Daridorexant was administered orally to pregnant rabbits during the period of organogenesis at doses of 30, 60 and 120 mg/kg/day, which are approximately 3, 4, and 10 times the MRHD of 50 mg, respectively, based on AUC. Daridorexant did not cause any fetal toxicity or malformation at doses up to 120 mg/kg/day. Daridorexant caused maternal toxicities of decreased weight gain and food consumption at the dose of 120 mg/kg/day. The NOAELs for maternal and fetal toxicity are 60 and 120 mg/kg/day, respectively, which are approximately 4 and 10 times the MRHD of 50 mg, respectively, based on AUC.

Daridorexant was administered orally to pregnant rats during gestation and lactation at doses of 50, 100, and 300 mg/kg/day, which are approximately 1, 3, and 9 times the MRHD of 50 mg, respectively, based on AUC. Daridorexant did not cause any maternal or developmental toxicities at doses up to 300 mg/kg/day. The NOAEL for maternal and developmental toxicity is 300 mg/kg/day, which is approximately 9 times the MRHD of 50 mg, based on AUC.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child-bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Non-specific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group (i.e., registry study)

☒ Pregnancy registry with external comparison group (i.e., registry study)

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review (i.e., complementary study)

☒ Electronic database study without chart review

☒ Other, please specify: Alternative study designs would be considered: e.g., a case control study or a retrospective cohort study using claims or electronic medical record data (i.e., complementary study)

2.4. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population

☐ Exposures

☒ Outcomes

☐ Covariates

☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: FDA's Active Risk Identification and Analysis (ARIA) lacks access to medical records. The proposed pregnancy registry study will require an expert clinical geneticist or dysmorphologist to review and classify medical records of all major congenital malformations. The complementary study using claims or electronic medical data may be algorithm-based. If the study shows an imbalance in any of the outcomes being investigated, FDA may require outcome validation in the selected database(s) or a chart-confirmed analysis.

Analytical Tools: ARIA data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal and fetal outcomes.

2.5. Proposed PMR language in the integrated clinical review.

The Division of Psychiatry requests two PMR studies (PMR 4150-2 and PMR 4150-3) related to pregnancy outcomes; the proposed language, as of December 3, 2021, is as follows:

> "Conduct a prospective, registry-based cohort study that compares the maternal, fetal, and infant outcomes of women exposed to daridorexant during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life."
>
> "Conduct an additional pregnancy study that uses a different observational design from the pregnancy registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to daridorexant during pregnancy compared to an unexposed control population."

References

1. Wyszynski, D.F. and K.E. Shields, *Frequency and type of medications and vaccines used during pregnancy.* Obstetric medicine, 2016. **9**(1): p. 21-27.
2. Dinatale, M. *The pregnancy and lactation labeling rule (PLLR)*. 2016 [cited 2021 September 9]; Available from: https://www.fda.gov/media/100406/download.
3. Krystal, A.D., *Insomnia in women.* Clinical cornerstone, 2003. **5**(3): p. 41-50.
4. Taylor, D.J., et al., *Epidemiology of insomnia, depression, and anxiety.* Sleep, 2005. **28**(11): p. 1457-1464.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 22, 2021
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 214985
Product Name and Strength:	Quviviq (daridorexant) tablets, 25 mg and 50 mg
Applicant/Sponsor Name:	Idorsia Pharmaceuticals Ltd (Idorsia)
OSE RCM #:	2021-98-1
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 21, 2021 for Quviviq. Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Quviviq (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and in response to the additional comments we send to the Applicant via email communication dated December 16, 2021.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Holmes, L. Label and Labeling Review for Quviviq (NDA 214985). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 NOV 23. RCM No.: 2021-98.

Reference ID: 4909782

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 21, 2021

Container labels and Carton labeling available in EDR at:
\\CDSESUB1\evsprod\NDA214985\0038\m1\us\114-labeling\draft\carton-and-container

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 14, 2021

TO: Zimri Yaseen, M.D.
Division of Psychiatry (DP)

Jasmeet Kalsi, Regulatory Project Manager, (DP)

Kim Updergraff, Associate Director for Labeling, (DP)

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for QUVIVIQ (daridorexant) tablets, for oral use

NDA: 214985

In response to DP consult request dated February 02, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Quviviq (daridorexant) tablets, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DP (Jasmeet Kalsi) on December 01, 2021, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on December 06, 2021.

Carton and Container Labeling:
OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 13, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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SAMUEL A FASANMI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 6, 2021
To:	Jasmeet (Mona) Kalsi, PharmD, RAC Senior Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samuel Fasanmi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	QUVIVIQ (daridorexant)
Dosage Form and Route:	Tablets, for oral use
Application Type/Number:	NDA 214985
Applicant:	Idorsia

1 INTRODUCTION

On January 8, 2021, Idorsia submitted for the Agency's review an original New Drug Application (NDA-214985) for QUVIVIQ (daridorexant) tablets, for oral use.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on March 4, 2021 and February 2, 2021, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Medication Guide (MG) for QUVIVIQ (daridorexant) tablets, for oral use. The patient labeling for QUVIVIQ (daridorexant) tablets, for oral use, was originally submitted as a Patient Package Insert (PPI), but on December 1, 2021, DP informed DMPP-OPDP that the patient labeling had been converted to a Medication Guide for consistency with other approved class labeling.

2 MATERIAL REVIEWED

- Draft QUVIVIQ (daridorexant) MG received on January 8, 2021and received by DMPP and OPDP on December 1, 2021.
- Draft QUVIVIQ (daridorexant) Prescribing Information (PI) received on January 8, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 1, 2021.
- Approved DAYVIGO (lemborexant) Tablets comparator labeling dated December 20, 2019.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 23, 2021
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 214985
Product Name and Strength:	Quviviq (daridorexant) tablets, 25 mg and 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Idorsia Pharmaceuticals Ltd (Idorsia)
FDA Received Date:	January 8, 2021 and October 4, 2021
OSE RCM #:	2021-98
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

Reference ID: 4893976

1 REASON FOR REVIEW

As part of the approval process for Quviviq (daridorexant) tablets, the Division of Psychiatry (DP) requested that we review the proposed Quviviq prescribing information (PI), container labels, blister labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Labels and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review *We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 ASSESSMENT AND RECOMMENDATIONS

To assess the proposed product packaging, labels and labeling, an information request was sent to Idorsia on September 28, 2021[a] requesting physical samples of the 25 mg and 50 mg professional sample packaging. In response, Idorsia provided physical samples of the professional sample blister wallet carton.

(b) (4)

Additionally, Idorsia submitted updated blister wallet carton labeling on October 4, 2021 to the NDA.

(b) (4)

[a] Wilson, L. "FDA Communication: NDA 214985: Daridorexant -- DMEPA Information Request" Message to Bradford Perry. Silver Spring (MD): FDA, CDER, OND, DP (US); 2021 SEP 28.

(b) (4)

We find that the proposed container labels, blister labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Idorsia Pharmaceuticals Ltd. (b) (4)

Our review of the Prescribing Information did not identify areas of vulnerability that may lead to medication errors.

4 RECOMMENDATIONS FOR IDORSIA PHARMACEUTICALS LTD

Table 2. Identified Issues and Recommendations for Idorsia Pharmaceuticals Ltd (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Comments for All Labels and Labeling			
(b) (4)			

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APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Quviviq that Idorsia Pharmaceuticals Ltd submitted on January 8, 2021.

Table 3. Relevant Product Information for Quviviq	
Initial Approval Date	N/A
Active Ingredient	daridorexant
Indication	Treatment of adult patients with insomnia (b) (4)
Route of Administration	Oral
Dosage Form	Tablets
Strengths	25 mg and 50 mg
Dose and Frequency	The recommended dose of Quviviq for adults is one tablet of 50 mg, taken orally in the evening within 30 minutes before going to bed. Quviviq can be taken with or without food, however sleep onset may be delayed if taken with or soon after a high-fat and high-calorie meal. Co-administration with Moderate CYP3A4 Inhibitors The recommended dose of Quviviq is 25 mg when used with moderate CYP3A4 inhibitors. Co-administration with Strong CYP3A4 Inhibitors Concomitant use of Quviviq with strong inhibitors of CYP3A4 is not recommended. Dosage Recommendations for Patients with Hepatic Impairment The recommended dose of Quviviq is 25 mg in patients with moderate hepatic impairment. Quviviq is not recommended in patients with severe hepatic impairment.
How Supplied	Bottles of 30 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Container Closure	Child-resistant cap

Reference ID: 4893976

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Quviviq labels and labeling submitted by Idorsia Pharmaceuticals Ltd on January 8, 2021 (except as noted).

- Bottle Labels
- Bottle Carton labeling ((b) (4))
- Professional Sample Blister Foil ((b) (4))
- Professional Sample Blister Carton ((b) (4))
- Professional Sample Blister Foil for Wallet
- Professional Sample Blister Wallet Carton (received on October 4, 2021)
- Prescribing Information (image not shown), available from \\CDSESUB1\evsprod\nda214985\0001\m1\us\114-labeling\draft\annotated\proposed-annotated.pdf

F.2 Labels and Labeling Images (not to scale)

Bottle Labels

(b) (4)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Clinical Inspection Summary

Date	10/14/2021
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Latrice Wilson, Pharm.D., Regulatory Project Manager Zimri Yaseen, M.D., Clinical Reviewer Pamela Horn, M.D., Clinical Team Leader Division of Psychiatry Products (DPP)
NDA #	214985
Applicant	Idorsia Pharmaceuticals Ltd
Drug	Daridorexant
NME	Yes
Therapeutic Classification	Dual Orexin Receptor Antagonist
Proposed Indication	Treatment of Insomnia
Consultation Request Date	03/11/2021
Initial Summary Goal Date	10/08/2021
Extended Summary Goal Date	11/08/2021
Action Goal Date	01/07/2022
PDUFA Date	01/08/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators (CIs), Drs. Gotfried, Heller, Ahmad and Thein were inspected in support of this original New Drug Application (NDA 214985) for daridorexant for the treatment of insomnia (b) (4) (Protocols ID-078A301 and ID-078A302).

Two complaints (# (b) (4) and # (b) (4) against Dr. Heller were investigated for Study ID-078A301 (see details below), and no evidence of subject safety or data integrity issues was identified to support the allegations. Although the inspection was not able to verify any of the allegations in the two complaints, we would recommend a sensitivity analysis regarding this site.

Overall, based on the results of these inspections, the conduct of the above studies was adequate, and the clinical data generated from these CI sites appear to be reliable in support of this NDA.

II. BACKGROUND

Daridorexant (proprietary name: Quviviq; code name: ACT-541468) is a dual orexin receptor antagonist, acting on both orexin 1 and orexin 2 receptors. It antagonizes the wakeful actions of orexin A and orexin B on orexin receptors and therefore decreases wakefulness and helps sleep.

The sponsor, Idorsia Clinical Development US Inc., has been developing daridorexant for the treatment of insomnia disorder. The clinical evidence of the efficacy and safety of daridorexant in the treatment of insomnia primarily came from two Phase 3 randomized, double-blind, placebo-controlled multi-center clinical trials (Protocols ID-078A301 and ID-078A302).

Clinical investigator (CI) inspections were conducted for both Study ID-078A301 and Study ID-078A302. These two studies had an identical design except for the daridorexant dose. The following is a brief description of these two studies.

Protocol ID-078A301 & Protocol ID-078A302

Title: "Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 in adult and elderly subjects with insomnia disorder"

Differences in Study ID-078A301 and Study ID-078A302

	ID-078A301	ID-078A302
Subjects Randomized (n)	930	924
Study Sites	Conducted at 75 sites in 10 countries (AUS, CAN, CZE, DEU, DNK, ESP, ITA, POL, SRB, USA)	Conducted at 81 sites in 11 countries (BEL, BGR, CAN, CZE, DEU, FIN, FRA, HUN, KOR, SWE, USA)
Study Initiation and Completion Dates	4 June 2018, 25 February 2020	29 May 2018, 14 May 2020
Daridorexant Dose	25 mg, 50 mg	10 mg, 25 mg

The primary study objective of these two studies was to evaluate the safety and efficacy of daridorexant 10 mg, 25 mg, and 50 mg on sleep parameters in subjects with insomnia disorder.

These were Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies evaluating the safety, tolerability, and efficacy of daridorexant in adult and elderly subjects with insomnia disorder. The study included the following four phases:

- A screening phase to characterize the population, including a 13- to 24-day patient-blind placebo run-in period to establish a reliable Baseline.
- A 12-week (84-day) double-blind, placebo-controlled, randomized treatment phase to assess the treatment effect.
- A 7-day patient-blind placebo run-out period to assess potential withdrawal symptoms and risk of rebound insomnia, enough to cover more than 5 half-lives of daridorexant.
- A 30-day follow-up period to collect safety information. Subjects who entered the double-blind extension study (ID-078A303) after the placebo run-out period did not require a safety follow-up period.

Randomization was stratified by the age groups (<65 and ≥65 years). Eligible subjects were randomized 1:1:1 to daridorexant low dose, high dose or placebo. For Study ID-078A301, the low dose was 25 mg and the high dose was 50 mg. For Study ID-078A302, the low dose was 10 mg and the high dose was 25 mg. Treatment was administered orally once a day at bedtime at home. During the polysomnogram (PSG) nights in the sleep laboratory, treatment was administered at least 2 hours after the last meal and 30 minutes before lights-off.

The primary efficacy endpoints for both studies were the change from Baseline to Month 1 and Month 3 in Latency to Persistent Sleep (LPS) and Wake After Sleep Onset (WASO), measured by PSG in a sleep laboratory as shown in the following:

- Change from Baseline to Month 1 in LPS (sleep onset).
- Change from Baseline to Month 3 in LPS.
- Change from Baseline to Month 1 in WASO (sleep maintenance).
- Change from Baseline to Month 3 in WASO.

LPS is a measure of sleep induction and WASO is a measure of sleep maintenance. The Baseline value was the mean of the two PSG nights at Visit 3. The Month 1 and Month 3 value was the mean of the two PSG nights at Visit 6 and Visit 8, respectively.

Secondary efficacy endpoints included patient-reported Total Sleep Time (sTST), estimated every morning at home using Sleep Diary Questionnaire (SDQ), and patient-reported daytime functioning, assessed using Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), every evening at home, as follows:

- Change from Baseline to Month 1 in sTST.
- Change from Baseline to Month 3 in sTST.
- Change from Baseline to Month 1 in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score.
- Change from Baseline to Month 3 in IDSIQ sleepiness domain score

Rationale for Site Selection

The clinical sites were chosen using a risk-based approach primarily based on numbers of enrolled subjects, treatment effect, protocol deviations, and prior inspection history.

For Dr. Heller, there were following complaints for Study ID-078A301: The sponsor reported that they received an anonymous complaint alleging the following non-compliance (Complaint #100045): lack of CI oversight, study staff were not qualified and improper administration of IP infusions, blood draw, urine collections, adverse event assessments.

In addition, there was another anonymous complaint for the same study alleging that Dr. Heller and staff allowed randomized subjects to use heroin during overnight study visits and supplied subjects with needles and syringes sometimes to ensure that subjects would not discontinue the study (Complaint #100140).

III. RESULTS

1. Mark Gotfried, M.D

Site # 3596
5750 West Thunderbird Building E 500
Glendale, AZ 85306
Inspection dates: May 24-28 and June 1, 2021

At this site for Protocol ID-078A302, 99 subjects were screened, 31 were enrolled, and 30 subjects completed the study. One subject (# (b) (6) in daridorexant 10 mg group) was discontinued due to the AEs of “dizziness” and “increased daytime sleepiness,” which were reported to FDA.

The inspection reviewed the informed consent forms for all 99 screened subjects as well as the source records for 31 enrolled subjects and 10 subjects with screen failures. The source records reviewed included, but not limited to, inclusion/exclusion criteria; randomization; blinding; dosing

and study drug administration; the primary and secondary efficacy endpoint parameters; adverse event reporting; and protocol compliance. The study monitoring, ethics committee approval and communications, financial disclosures, FDA 1572s, study staff background and training were also reviewed during the inspection.

The primary and the secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

2. **Barry Heller, M.D.**
   Site # 3575
   2008 Pacific Ave
   Long Beach, CA 90806
   Inspection dates: May 17-20, 2021

At this site for Protocol ID-078A301, 142 subjects were screened, and 123 subjects had screen failures prior to the run-in period. After the run-in period, five subjects withdrew consent, and two subjects were lost to follow up. In the end, twelve subjects were enrolled and randomized, and 11 subjects completed the study. One subject (# (b) (6) in in daridorexant 50 mg group) was discontinued due to a drug related adverse event of decreased renal function, which was reported to FDA. This subject was also found to have taken a prohibited medication (Trazadone) during the study, which was reported as a protocol deviation.

The inspection reviewed 25% of informed consents of the 142 screened subjects during the study. All 12 randomized subjects' records were reviewed. These records included, but were not limited to, study eligibility criteria, concomitant medications, the primary and the secondary efficacy endpoint data, adverse events, and protocol deviations. Other records reviewed during the inspection included shipping records and receipt of the study drug as well as the drug storage records; files of communication between Dr. Heller and the sponsors for content; monitoring correspondence and reports; Independent Review Board (IRB) approvals; training records; delegation of authority logs; FDA Form 1572s; and financial disclosures.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. The complaints (Complaints # (b) (4) and # (b) (4) were investigated, and no evidence of subject safety or data integrity issues was identified to support the allegations.

Reviewer's comment: Although the inspection was not able to verify any of the allegations in the two complaints, we would recommend a sensitivity analysis regarding this site.

3. **Maha Ahmad, M.D.**
   Site # 3505
   423 W 55th Street 4th Floor
   New York, NY 10019
   Inspection dates: August 9 - 13, 2021

At this site for Protocol ID-078A301, 92 subjects were screened, 25 were enrolled, and 24 subjects completed the study. One subject withdrew consent due to a scheduling conflict.

The inspection reviewed the informed consent forms and study eligibility for all 92 screened subjects. In addition, the inspection reviewed the primary and secondary endpoint data, adverse events, and concomitant medication logs for all 24 subjects who completed the study. The

laboratory results were randomly audited. The regulatory records reviewed included, but were not limited to, blinding, ethics committee approval and communications, financial disclosures, FDA 1572s, study staff background and training.

The primary and the secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

4. **Stephen Thein, M.D.**
   Site # 3550
   3003 Fourth Ave
   San Diego, CA 92103
   Inspection dates: June 14-18, 2021

At this site for Protocol ID-078A302, 134 subjects were screened, 53 were enrolled, and 48 subjects completed the study. Five subjects discontinued the study. The subjects and the reasons for discontinuations were verifiable, i.e, there were no discrepancies between the source records and the line listings submitted by the sponsor for discontinuations.

The inspection reviewed 47 out of the total of 53 enrolled subjects' source records, which included, but were not limited to, informed consent forms (ICFs); case report forms (CRFs); medical records for office visits and hospital visits; the primary and secondary endpoint data - the polysomnography (PSG) recordings and reports; adverse events; laboratory reports; electronic subject diaries (e-Diaries); and electrocardiogram (ECG) tracings and reports. Other records reviewed included drug accountability records; site correspondence with the sponsor, monitor and institutional review board (IRB); and regulatory records, including FDA 1572s and financial disclosure records.

The primary and the secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

The inspection found one discrepancy between the source record and the line listing for the result of urine drug screening. Specifically, Subject #(b) (6) (in daridorexant 25 mg group) tested positive for tetrahydrocannabinol (THC) at Visit 10 according to the source record, but this was not recorded in line listing.

Reviewer's comment: Since the primary efficacy endpoints were LPS and WASO changes from Baseline (Visit 4) to Month 1 (Visit 6) and Month 3 (Visit 8), respectively, Subject #(b) (6) testing positive for THC at Visit 10 during the Follow-up Phase would not be expected to have an impact on the study efficacy or safety results.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Office of Scientific Investigations

cc:
DARRTS: NDA 214985
DP/Project Manager/Latrice Wilson
DP/Division Director/Tiffany Farchione
DP/Medical Officer/Zimri Yaseen
DP/Clinical Team Leader/Pamela Horn
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENN W SELLERS
10/14/2021 08:41:45 AM

PHILLIP D KRONSTEIN
10/14/2021 08:46:00 AM

KASSA AYALEW
10/14/2021 09:49:51 AM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 30, 2021

To: Tiffany Farchione, MD, Director
Division of Psychiatry

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Edward Hawkins, PhD, Pharmacologist
Controlled Substance Staff

Subject: **Product name:** Quviviq (Daridorexant (ACT-541468))
Dosages, formulations, routes: 25 and 50 mg oral tablets
NDA number: 214985
IND Number: 128789
Indication(s): Adult patients with insomnia (b) (4)
PDUFA Goal Date: January 8, 2022

Materials Reviewed:

- NDA 214985 for Quviviq (Daridorexant), submitted January 8, 2021, and subsequent amendments

Table of Contents

I. SUMMARY

1. Background

This memorandum is in response to a consult request from the Division of Psychiatry (DP) to evaluate abuse-related preclinical and clinical data submitted by Idorsia Pharmaceuticals Ltd (Applicant) under NDA 214985 and IND 128789 for Quviviq (daridorexant (ACT-541468)). The Applicant submitted a 505(b)(1) application, and DP would like CSS to review the abuse-related data submitted as part of the NDA. The IND was first seen by CSS on December 4, 2017, when comments regarding the design of the nonclinical abuse plan were sent to the Applicant.

Daridorexant is a dual orexin receptor antagonist that functions as a central nervous system depressant with a proposed indication of (b) (4) adult patients with insomnia. The drug is designed as film-coated tablets of 25 mg and 50 mg with the highest proposed therapeutic dose of 50 mg/night 30 minutes before bedtime. The Applicant conducted an abuse potential assessment consisting of in vitro and in vivo nonclinical studies, as well as a human abuse potential study.

In the NDA submission, the Applicant proposes that daridorexant should be controlled under schedule V of the Controlled Substances Act (CSA). After evaluating the nonclinical and clinical data in the NDA, CSS does not agree with the Applicant and concludes that daridorexant has a potential for abuse that is lower than substances in Schedule III but greater than placebo. Therefore, CSS recommends daridorexant be controlled under schedule IV of the CSA.

2. Conclusions

Reference ID: 4866112

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 214985 for daridorexant and concludes that the drug has abuse potential and should be controlled in schedule IV under the CSA. This conclusion is based on the following data:

- Daridorexant is a new molecular entity whose primary mechanism of action is as a dual orexin receptor antagonist. This mechanism of action is similar to other orexin antagonists controlled under schedule IV (i.e., suvorexant and lemborexant).

- Daridorexant is slightly more potent at the orexin 1 receptor with a K_b = 0.47 nM compared to the orexin 2 receptor with a K_b = 0.93 nM. The major active metabolites of daridorexant, M1, M3, and M10 are not expected to produce appreciable clinical effects.

- In animal behavior and toxicity studies, daridorexant was shown to be brain penetrant and demonstrated dose-dependent decreases in general and locomotor activity as well as a decrease in body temperature.

- In the self-administration study conducted in Sprague-Dawley rats, daridorexant was not self-administered and did not appear to produce reinforcing effects. These results are consistent with that of other dual orexin antagonists, namely suvorexant and lemborexant. It is possible that dual receptor orexin antagonists may be self-administered under a different or restricted set of experimental conditions.

- The Applicant conducted two drug discrimination studies:

    - In the first study, rats were unable to reliably distinguish the suvorexant cue from vehicle after 81 training sessions that were divided into three separate phases.
    - In the second study, rats were trained to distinguish zolpidem, a gamma-amino butyric acid (GABA) receptor positive allosteric mediator (PAM) from vehicle. In the generalization phase, the maximum mean percent responding at all of the doses tested was 5.1% with no significant effect on the rate of responding. These data indicate that daridorexant did not generalize to the stimulus cue of zolpidem.

- In a human abuse potential study, the highest therapeutic dose of daridorexant produced drug liking scores statistically lower than the positive comparators, zolpidem (CIV) and suvorexant (CIV), but statistically higher than placebo. Doses of daridorexant that were 2- and 3-fold the highest therapeutic dose produced drug liking scores that were not statistically different from supratherapeutic doses of the positive comparators.

- Daridorexant does not appear to produce signs of physical dependence or produce withdrawal upon abrupt cessation in clinical trials.

- An analysis of CNS-mediated adverse events (AEs) that can be indicative of abuse liability was conducted on the clinical studies provided by the Applicant. This analysis indicated that the most prevalent AEs were somnolence, fatigue, and dizziness.

Reference ID: 4866112

3. Recommendations

Based on an analysis of the data provided in NDA 214985, CSS recommends that:

1. Daridorexant should be controlled in schedule IV under the Controlled Substances Act.
    a. CSS will notify the Applicant of this decision before the PDUFA date.

2. Section 9 (Drug Abuse and Dependence) should reflect the abuse-related data submitted in the NDA and previous safety labeling requirements for this class of drugs. CSS recommends the following changes to the Applicant's label, where **additions are indicated in bold underlined text** and deletions have been stricken through:

9 DRUG ABUSE AND DEPENDENCE

Reference ID: 4866112

(b) (4)

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Daridorexant is the active pharmaceutical ingredient in Quviviq (daridorexant (ACT-541468)). Daridorexant is formulated as film-coated tablets of 25 mg and 50 mg with the highest therapeutic dose

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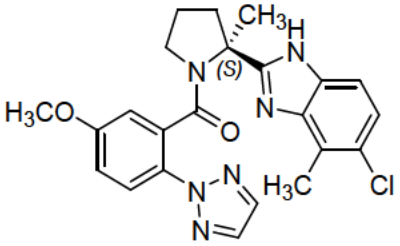
(b) (4)

The following footnotes are from the drug label and should be deleted:

(b) (4)

of 50 mg once per night 30 minutes before bedtime. Daridorexant, also known by the developmental code ACT-541468 is the nonproprietary name of [(S)-2-(5-chloro-4-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl](5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone. Daridorexant has a molecular weight of 450.93 g/mol, a chemical formula of $C_{23}H_{23}ClN_6O_2$, and a CAS # of 1505484-82-1 (free base). The drug substance is a white to off-white powder that is freely soluble in acidic water, sparingly soluble in dimethylsulfoxide (DMSO) and methanol, and only slightly soluble in ethanol (Table 1). Daridorexant is not currently listed in a schedule of the CSA.

Table 1: General Chemical Properties of Daridorexant

Nomenclature	
International Non-proprietary Name (INN)	Daridorexant
Chemical Abstract Number (CAS)	1505484-82-1 (free base)
Chemical Name (IUPAC)	[(S)-2-(5-chloro-4-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl](5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
Drug product codes	ACT-541468
Schedule in the CSA	not current controlled
Structure	
Molecular Formula	$C_{23}H_{23}ClN_6O_2$
Molecular mass	450.93 g mol^{-1} (free base)
Structure	
General Properties	
Appearance	White to almost white crystalline powder
pKa	pKa1 = 1.3; pKa2 = 11.5
Solubility (25°C)	soluble in acidic water, slightly soluble in ethanol
Chiral form	Single stereoisomer with one chiral center

The manufacturing process of daridorexant is described in section S.2.2 which indicates [redacted] (DMF # [redacted]).

Excipients in the tablet

The drug product contains a series of excipients (b) (4). The tablets are manufactured in dose strengths that contain 25 mg and 50 mg of the active ingredient (i.e., daridorexant). The excipients and their functions in the 50 mg tablet are listed in Table 2. The excipients in Quviviq do not have a known abuse liability.

Table 2: Composition of Excipients Used to Manufacture Daridorexant 50 mg

Material	Function	50 mg Strength (mg)
(b) (4)		
Daridorexant	Active ingredient	50.00
Mannitol		(b) (4)
Povidone (b) (4)		
Microcrystalline Cellulose, (b) (4)		
(b) (4)		
Croscarmellose sodium		
Silicon Dioxide		
Magnesium Stearate		
(b) (4)		

1.2 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

The Applicant is not seeking abuse-deterrent labeling and did not conduct manipulation or extraction studies to assess the abuse-deterrent properties of Quviviq.

2. Nonclinical Pharmacology

2.1 Receptor Binding and Functional Assays

The Applicant conducted several studies to assess the primary and secondary pharmacology of daridorexant. These studies determined that daridorexant is a selective dual orexin receptor antagonist (DORA) that inhibits the orexin neuropeptide-induced activation of the orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R) subtypes.

The Applicant conducted two studies to assess the in vitro binding of daridorexant at orexin receptors and off-target receptors (Study #s B14.010 and B20.019). Study # B14.010 determined that daridorexant is an insurmountable antagonist of OX1R and OX2R using calcium mobilization as measured via a fluorometric imaging plate reader (FLIPR) assay (Table 3). The data in Table 3 indicate

that daridorexant has a similar potency and duration of action as suvorexant at OX1R, however, it is more potent and has double the occupancy time as suvorexant at OX2R.

Table 3: Antagonistic Potency of Daridorexant at the Human Orexin Receptors

	OX1R K_b (nM)	**Receptor Occupancy $t_{1/2}$ (min)**	**OX2R K_b (nM)**	**Receptor Occupancy $t_{1/2}$ (min)**
Daridorexant	0.47	46	0.93	87
Suvorexant	0.3	31	0.61	43

Study # B-14.063 was conducted to determine the off-target binding affinity of daridorexant to a receptor panel that includes receptors and transporters associated with having a potential for abuse. This study found that daridorexant, at a dose of 10 µM, produced 52% inhibition of the dopamine transporter (DAT). Daridorexant did not produce significant binding at other receptors, transporters, or ion channels that are commonly associated with abuse liability.

As a follow-up, the Applicant conducted Study # B-20.057 to determine if daridorexant had any activity at the DAT. This study concluded that the drug produced antagonist activity with an IC_{50} of 14.3 µM at the DAT.

Metabolites

Three major metabolites were identified in humans: M1 (ACT-776537), M3 (ACT-776063), and M10 (ACT-1016-3307) (Study # D-17.128). Study # B-17.052 was conducted to determine the in vitro potency of these metabolites measuring calcium mobilization through a FLIPR assay. The M1, M3, and M10 metabolites had 40- to 1545-fold lower potency than daridorexant at human OX1R and 8- to 555-fold lower potency at human OX2R (n = 3). Considering the low potency of the metabolites along with the low predicted free fraction in human plasma (0.25 ng/mL at Tmax for M1), it is unlikely these metabolites contribute to the clinical effects produced by daridorexant. Therefore, the metabolites were not directly assessed for their abuse potential.

Conclusion

Daridorexant is a dual orexin receptor antagonist that is more potent at the OX1R than the OX2R, however, it has double the receptor occupancy $t_{1/2}$ at OX2R (87 min.) compared to OX1R (46 min). The data also indicate that the drug may have some inhibitory activity at DAT, however, the behavioral effect of this activity is unclear. The M1, M3, and M10 metabolites are not expected to produce clinical effects.

2.3 Findings from Safety Pharmacology and Toxicology Studies

The Applicant conducted a series of safety studies to assess the pharmacology and pharmacokinetics (PK) of daridorexant.

CNS mediated behaviors

Reference ID: 4866112

In study B-14.036 male Wistar rats were given single oral doses of 10, 30, 100, and 300 mg/kg daridorexant and drug plasma, CSF, and brain concentrations were tested 1, 3, 6, and 24 hours after administration. The time points of the sample collections in this study were determined to provide a representation of the drug's effects on the sleep-wake cycle of the animal. These time points are not suitable for determining the PK parameters of daridorexant because there is too much time between the measurements. The take-away from these studies is that daridorexant does penetrate the blood brain barrier and produced brain-to-plasma ratios of 2.1 to 2.2 one-hour post administration.

The Applicant conducted behavioral safety assessments starting with an Irwin screen (Study # T-13.223) to assess the central nervous system effects of daridorexant. In this study, male Wistar rats received single oral doses of 0, 100, 300, and 1000 mg/kg drug. All doses produced a transient decrease in rectally measured body temperature as well as an increased incidence of whole-body tremors. When rats were left unstimulated there was also a dose-dependent reduction in activity which was expected considering the proposed indication. The no-observed-adverse-effect-level was considered to be 1000 mg/kg as there were no signs that affected the global health of the animals. The effects of daridorexant on locomotor activity were also measured in Study # B-14.058. Rats given a single oral dose of 300 mg/kg presented with a 63% decrease in locomotor activity compared to their vehicle control group.

The Applicant also conducted studies on the effects of daridorexant (0, 100, 300, 1000 mg/kg PO) on the respiratory system using whole-body plethysmography in conscious male Wistar rats. Daridorexant did not alter any of the measured parameters of respiratory function.

Pharmacokinetics

An analysis of the PK profile of daridorexant in rats and beagle dogs through both single oral and intravenous dosing (Study # B-13.116) was also conducted. Intravenous doses of 0.1, 0.3, and 1 mg/kg were administered to rats and 0.3, 1, and 3 mg/kg to dogs infused over the course of 5 to 15 minutes. The oral doses were 3, 10, and 30 mg/kg in rats and 1, 3, 10, and 30 mg/kg in dogs. The animal abuse potential assessment was conducted in rats; therefore, this section of the review will focus on the rat data. This assessment will only include the relevant doses (e.g., lowest and highest doses tested) for analysis rather than a complete review of the PK. For a complete assessment of the nonclinical PK of daridorexant see the pharm/tox portion of the unified NDA review. The data presented in Tables 4 through Table 6 were obtained in male Wistar rats. The data in Table 4 indicate that the clearance rate of daridorexant is relatively constant over the tested doses and is therefore, independent of dose. However, the half-life increased with dose ranging from 0.5h to 2.1h and the exposure of daridorexant increased dose proportionally as measured by AUC.

Table 4: PK Parameters in Fasted Male Wistar Rats After IV Administration of Daridorexant

	Dose (mg/kg)	**Mean**	**Range**
$AUC_{0\text{-}inf}$ (ng·h/mL)	0.1	23.2	21.2-27.0
	1	226	197-257
CL (mL/min·kg)	0.1	72	62-79
	1	74	65-85

Reference ID: 4866112

$t_{1/2}$ (h)	0.1	0.5	0.3-0.7
	1	2.1	1.3-4.5

The data presented in Table 5 indicate that daridorexant is quickly orally absorbed independent of the tested doses with a T_{max} of 0.3h and a bioavailability of 10 to 17% in the fasted state. Similar to IV administration, the C_{max} increases dose proportionally leading to a linear increase in exposure as measured by AUC.

Table 5: PK Parameters in Fasted Male Wistar Rats After Oral Administration of Daridorexant

	Dose (mg/kg)	**Mean**	**Range**
Cmax (ng/mL)	3	61.4	46.7-84.7
	30	721	458-1390
Tmax (h)	3	0.3	0.3-4.0
	30	0.3	0.5-1.5
$AUC_{0\text{-}inf}$ (ng·h/mL)	3	69.5	48.9-88.0
	30	1140	891-2010

The effect of food on PK parameters was assessed in beagle dogs in Study # B-13.116 in which animals were fed 30-minutes before being administered daridorexant 10 mg/kg PO. According to the data in Table 11, the mean C_{max} and AUC increased by 30%, resulting from a mean increase in oral bioavailability (fasted: 45% and fed: 58%). Absorption with food did not significantly alter the T_{max}. These data indicate that food may increase the bioavailability of daridorexant in humans.

Table 6: Fed and Fasted Rat PK Parameters Orally Administered Daridorexant (10 mg/kg)

Oral	**Dose (mg/kg)**	**Fed**	**Fasted**
Cmax (ng/mL)	10	1410	652
Tmax (h)	10	2.5	2.0
$AUC_{0\text{-}inf}$ (ng·h/mL)	10	9710	6940

The effect of sex on PK parameters was also tested in the IV and oral treatment groups. Peak plasma concentrations and exposures were 1.6-fold and 3.0-fold higher in female rats compared to males. This appeared to be the result of a 30% higher bioavailability in the female rats. There were no consistent sex differences observed in dogs in the toxicity studies. This may indicate that the sex differences observed in the rat are species dependent.

The Applicant also conducted a study to determine the exposure of daridorexant after multiple oral doses in a 4-week toxicity study (Study # T-13.221). In this study, male rats received oral daily doses of 100, 300, or 1000 mg/kg daridorexant and the drug exposure, as measured by AUC, was determined on day 1 and day 28 of the study. The data presented in **Error! Reference source not found.** indicate that

Reference ID: 4866112

after 28 days of dosing there was no change in exposure at the 100 mg/kg dose, however, there was a decrease of approximately 50% after 28 days of administration of the 300 and 1000 mg/kg doses.

Table 7: Exposure of Daridorexant in Male Rats After Multiple Dose Oral Administration

		$AUC_{0\text{-}24h}$ (µg·h/mL)	
Oral fasted	Dose (mg/kg)	Day 1	Day 28
$AUC_{0\text{-}inf}$ (ng·h/mL)	100	10.9	12.2
	300	61	32.1
	1000	171	78.1

Conclusion

Daridorexant is quickly absorbed orally and produces a dose-dependent linear increase in Cmax and exposure. The half-life of the drug increases with increasing dose which is likely the result of plasma protein binding and tissue compartmentalization. The bioavailability of the drug appears to be affected by food and is increased in the fed state, at least in dogs. Food and dose did not alter the Tmax which remained steady at 0.3h indicating that this is the proper time at which animals should be tested in abuse liability studies. Sex differences in PK parameters were observed in rats, however, they were not observed in dogs and the Applicant should be able to account for these differences in their abuse liability studies by increasing the dose in male rats as necessary.

2.4 Animal Behavioral Studies

Toxicity Studies

The Applicant did not conduct single-dose toxicity studies with daridorexant. However, 11 repeat-dose toxicity studies were conducted using mice, rats, or beagle dogs using the oral route of administration. Five studies were conducted using male and female Wistar rats who received doses ranging from 0 to 1000 mg/kg for 3 days to 4 weeks or doses of 0 to 450 mg/kg for 13 weeks or 26 weeks. The 4-week, 13-week, and 26-week studies were all followed by 4-week recovery periods that were used to assess physical dependence.

Study # T-13.144 was a three-day tolerability study in which rats were given oral doses of 1000 mg/kg/day daridorexant. The observed clinical effects consisted of salivation and reduced cage activity. The reduction of cage activity was observed in all of the toxicity studies and is most likely the result of the sleep promoting effect of the drug.

Study # T-13.163 was a two-week study in which rats were administered 0, 100, 300, 600 (females only), and 1000 mg/kg/day. Similar to the 3-day study, the clinical symptoms observed consisted of reduced cage activity and reduced food consumption at all doses. These results were similar in the 4-week study (Study # T-17.009) in which rats were given doses of 0 (vehicle), 100, 300, and 1500 mg/kg/day (500 mg/kg/day on Days 1–2; 1000 mg/kg/day on Days 3–4; 1500 mg/kg/day on Days 5–28).

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Studies T-14.068 and T-15.076 were 13-week and 26-week toxicity studies in rats followed by 4-week recovery periods. In both studies rats were orally administered doses of 0, 50, 150, and 450 mg/kg/day daridorexant. Clinical signs observed in both studies consisted of salivation, mouth rubbing, paddling, and reduced cage activity. As mentioned above, the reduction of cage activity was considered to be related to the sleep promoting effects of the drug and ceased after drug treatment.

Abuse-Related Studies

Drug Discrimination (Study #VPT7063)

Drug discrimination is an experimental method in which animals identify whether a test drug produces physical or behavioral effects (an interoceptive response) similar to those produced by another drug with known pharmacological properties. If the known drug is one with abuse potential, drug discrimination can be used to predict if a test drug will have abuse potential in humans (Balster and Bigelow, 2003). For abuse assessment purposes, an animal is first trained to press one bar when it receives a known drug of abuse (the training drug) and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug is more like the known drug of abuse or more like placebo. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing ≥80% on the bar associated with the training drug (Sannerud and Ator, 1995; Doat et al., 2003). A test drug that generalizes to a known drug of abuse will likely be abused by humans (Balster and Bigelow, 2003).

Study # VNG6680

In comments to the original study protocol submitted to the Agency as part of the End-of-Phase 2 meeting, the Agency requested that the study be conducted in animals trained to discriminate suvorexant from vehicle (November 16, 2017). In response to this, before conducting the drug discrimination study, the Applicant conducted Study # VNG6680 to determine if rats can learn to distinguish the interoceptive cue of suvorexant from vehicle. In this study, female Sprague-Dawley rats underwent a training procedure that began with food reinforcement for a fixed-ratio 1 (FR1) schedule of reinforcement. Rats then received vehicle or suvorexant on a pseudo-random alternation schedule of reinforcement with the goal of reaching an FR10 schedule of reinforcement. The progression for schedule advancement was FR1, FR2, FR5, and FR10 and animals were moved to the next schedule once they produced >80% lever correct responding in three consecutive sessions. Each session lasted for 30 minutes or until 100 reinforcements were delivered.

Training occurred over three phases, each of which consisted of 23 to 29 training sessions with one training session per day. In the first session, animals were administered 30 mg/kg one hour before training. Only one rat acquired an FR10 and the other ten were at an FR5 or below. In the second phase, the Applicant gave the animals 100 mg/kg suvorexant (one hour before training) to try and increase the suvorexant cue and a similar result occurred with only two animals acquiring an FR10 schedule of reinforcement. In the third phase, and owing to the long half-life of suvorexant, the last group of animals were administered 100 mg/kg two hours before training. In this group, nine out of ten animals achieved an FR10 with >80% responding on the correct lever in consecutive sessions.

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However, the data indicate that about half of the animals were giving their first response on the incorrect lever (five out of nine) after receiving test drug or vehicle. According to the study report, it was possible that the animals were not responding to the suvorexant cue but were actually responding to the first food reinforcement as being the first lever to respond to, independent of treatment. In order to test this hypothesis, a second criterion was introduced in which the animals had to press the non-correct lever four times before they received the first reinforcement during at least three consecutive sessions. Five out of nine rats failed to meet the second criterion despite continued training to FR10. After 81 total sessions, comprised of three phases the training sessions were halted. The total averaged plasma concentrations of suvorexant in rats treated at 30 mg/kg, reached levels between 288 nM at 1 h and 494 nM at 2 h after administration. When rats were treated at 100 mg/kg, suvorexant plasma levels reached 867 nM at 1 h and 1729 nM at 2 h after administration. The doses of suvorexant produced plasma levels that were 0.5 to 3.5-fold the Cmax of the highest approved dose of 20 mg (574 nM).

This study determined that, under these training conditions, the animals were unable to reliably distinguish the suvorexant cue from vehicle. As a result, the Applicant conducted a second study in which rats were trained to distinguish zolpidem from vehicle.

Study # VPT063

This study was conducted to determine if daridorexant produces an interoceptive cue similar to that of zolpidem in a two-choice drug discrimination procedure. Female Sprague Dawley rats were trained to distinguish zolpidem (3 mg/kg) from vehicle to an FR10 schedule of reinforcement with presses on the inappropriate lever not being reinforced. All treatments were administered 15 minutes before test sessions and the test sessions lasted for 30 minutes (Tmax range from 15 to 45 minutes). In baseline sessions, a dose-response curve for zolpidem was conducted using doses of 0.3, 0.56, 1, 1.8, and 3 mg/kg oral (gavage), in a cross-over design. Zolpidem produced a sigmoidal dose response curve confirming the discriminative stimulus ability of the rats to distinguish zolpidem from vehicle. Animals were then moved to the test sessions in which they were administered oral doses of 15, 30, or 60 mg/kg daridorexant in a cross-over design.

In this study, full generalization is considered when there is ≥ 80% responding on the drug appropriate lever and no generalization is associated with ≤ 20% responding on the drug appropriate lever. In the baseline sessions, the zolpidem treatment at 1 mg/kg produced partial generalization with a mean responding of 78.1% on the drug appropriate lever. The 1.8 mg/kg and 3 mg/kg treatment of zolpidem produced full generalization to the zolpidem cue (animals trained to 3 mg/kg) with respective mean percent responses of 97.8% and 99.6%. The rates of responding were not significantly affected by these doses of zolpidem. These data indicate that the animals were sufficiently trained to discriminate the stimulus effects of zolpidem (3 mg/kg) from vehicle.

In the generalization phase, the maximum mean percent responding at all of the doses tested was 5.1%. The percent responding on the zolpidem-appropriate lever after administration of daridorexant was: 0% for vehicle, 0.8% for 15 mg/kg, 0% for 30 mg/kg, and 0.8% for 60 mg/kg. The rates of responding were not affected significantly, however, there was a slight decrease from the vehicle treated animals (173.1 presses/min.) to the 60 mg/kg daridorexant treated animals (146.7 presses/min.). This decrease would not have affected the outcome of the study which clearly indicates that the animals did not substitute the interoceptive cues of zolpidem and daridorexant.

According to the Applicant, the doses of daridorexant used in the study produced C_{max} levels in rats that are approximately 6.05, 16.18, and 18.41-fold higher than the highest therapeutic dose (50 mg) produced in humans. These fold differences were determined by the data presented in Table 10 where each dose in rats produced a C_{max} value that was compared to the C_{max} produced by the highest therapeutic dose in humans (50 mg). The direct comparison produced a fold difference of 0.65, 1.74, and 1.98 for the doses of 15, 30, and 60 mg/kg daridorexant respectively. However, according to an in vitro clinical study, (Study # B-13.202) the unbound drug fraction in rats is 2.8% and in humans is 0.3% indicating that rats have a higher unbound exposure of the drug than humans. When the percent of unbound drug is taken into account the unbound fold-difference for each concentration is 6.05, 16.18, and 18.41. These numbers indicate that the drug was tested under a wide dose range, however, the animals were not tested to the point of being physically incapacitated by the drug.

Table 8: Determination of Fold-Difference for Plasma Levels Between Rat and Human in Drug Discrimination Assay

Dose (mg/kg/day)	**Rat**	**Human Cmax (ng/mL)**	**Fold-Difference**	**Unbound Fold-Difference**
	Cmax (ng/mL)	50 mg dose		
15	653	1006	0.65	6.05
30	1750	1006	1.74	16.18
60	1990	1006	1.98	18.41

Self-Administration (Study # VPT6870)

Self-administration is a method that assesses whether a drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug. Drugs that are self-administered by animals are likely to produce rewarding effects in humans, which is indicative of abuse potential. Generally, a good correlation exists between those drugs that are self-administered by animals and those that are abused by humans (Balster and Bigelow, 2003). It is notable that self-administration is a behavior that is produced by drugs that have been placed into every schedule of the CSA. Additionally, rates of self-administration for a particular drug will go up or down if the available drug dose or the work requirement (bar pressing for drug) is altered. Interpretation of the self-administration test results is that the data provide an abuse potential signal, suggesting that a drug has rewarding properties, but not necessarily that it produces more rewarding effects than another drug in humans.

The objective of this study was to assess the reinforcing properties of daridorexant in female Sprague, Dawley rats by determining if self-administration behavior was maintained when the drug was substituted for cocaine. Rats were implanted with a femoral vein catheter and trained to self-administer cocaine (0.8 mg/kg/infusion) to an FR10 schedule of reinforcement. After acquisition of the training stimulus, animals were switched to saline to demonstrate extinction of the self-administration behavior after removal of the cue (i.e., cocaine). After extinction, rats were re-exposed to cocaine under an FR10 schedule up to stable responding. Thirty-eight animals completed operant training and were divided into one of five treatment groups:

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1. Negative control: vehicle
2. 0.1 mg/kg/infusion daridorexant
3. 0.3 mg/kg/infusion daridorexant
4. 1 mg/kg/infusion daridorexant
5. Positive control: cocaine 0.8 mg/kg/infusion

The data obtained in this study indicate that the rats did not maintain responding when daridorexant was substituted for cocaine and that daridorexant does not produce reinforcing effects similar to cocaine. The data presented in Table 9 indicate that after the third baseline session (animals received cocaine 0.8 mg/kg/infusion for three sessions) there was no significant difference between the test groups. After the first substitution session, there was a significant decrease in lever presses which was maintained through repeated sessions. Substitution session number 6 (Table 9) indicates that the levels of responding for the daridorexant treated animals were not significantly different from the vehicle treated group, while the cocaine positive control animals maintained their response rates. Re-exposure of the animals to cocaine reinstated active lever responding to the pre-established cocaine reinforced levels. The bioanalytical report conducted to predict the plasma concentrations of the vehicle and daridorexant dose groups reported blood concentrations ranging from below the limit of quantification to 2660 ng/mL daridorexant. As determined from Table 8, this represents a blood concentration that is several fold that of the highest therapeutic dose in humans.

Table 9: Active Lever Presses During the Substitution Phase (Data obtained from NDA 214985, Study # VPT687, Table 2)

		Daridorexant (mg/kg/infusion)			**Cocaine (mg/kg/infusion)**
Session #	**Vehicle**	**0.1**	**0.3**	**1**	**0.8**
Baseline #3 (cocaine)	227.11 ± 21.20	224.89 ± 21.75	210.89 ± 7.39	230.00 ± 28.33	256.56 ± 40.15
Substitution #6	31.89 ± 5.44*	53.78 ± 6.53*	50.78 ± 11.70*	24.22 ± 5.99*	259.11 ± 30.07
Re-Exposure #3 (cocaine)	195.78 ± 23.55	241.33 ± 21.98	204.22 ± 19.76	223.44 ± 34.89	223.89 ± 32.99

*$p<0.01$, compared to cocaine baseline #3

Conclusion

Several studies were conducted to assess the behavioral effects of daridorexant. In repeat dose toxicity studies, sedative effects were observed in rats, consistent with the therapeutic indication of the drug. In a two-choice drug discrimination study, daridorexant did not substitute for the zolpidem cue, an expected finding considering the different mechanisms of action of the two drugs. The Applicant did try to conduct a drug discrimination study in which rats were trained to discriminate suvorexant from vehicle, however, the animals were unable to reliably discern the suvorexant cue. The Applicant also assessed the reinforcing effects of daridorexant in a rat self-administration assay. The rats in this assay produced vehicle levels of responding when given access to daridorexant which was significantly lower than the animals treated with the positive control cocaine. As a result, at the doses tested, these studies provide evidence that daridorexant does not produce reinforcing effects or stimulus effects similar to the schedule IV drug zolpidem.

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2.5 Tolerance and Physical Dependence Studies in Animals

Physical dependence is measured in animals through the induction of a withdrawal syndrome, typically spontaneously, although it can also be precipitated through the use of an antagonist. Study # VPT6831 was conducted in female Sprague Dawley rats who received oral doses of 0, 20, or 200 mg/kg/day daridorexant. This dose was maintained until Day 28 and was followed by a 14-day discontinuation period. The positive control group received chlordiazepoxide (CDP) which was orally administered and titrated up from 10 mg/kg/day to 200 mg/kg/day in daily increments of 10 mg/kg. The final dose of 200 mg/kg/day was maintained from Day 20 to Day 28. After 28 days the animals entered a discontinuation phase in which they were administered vehicle until Day 42 of the study (i.e., a 14-day withdrawal period). The animals were assessed on Days 1, 14, 25, 28 through 32, 35, 38, and 42 for physiological parameters, general clinical signs, and locomotor activity and neurobehavioral effects.

At the doses of the test drug used in this study, the maximal plasma concentrations of ~499 ng/mL and ~2920 ng/mL were achieved at the end of the treatment phase, which is approximately 0.5-fold and 2.9-fold above the human efficacious Cmax of 1006 ng/mL after a 50 mg dose.

No clinical signs or abnormalities were observed in the vehicle treated control group. During the drug treatment phase, there was slight hair loss in the drug treatment groups observed in one animal in the 20 mg/kg/day group and in two animals in the 200 mg/kg/day group. There were also indications of hunched posture, decreased body temperature, decreased locomotor activity, and piloerection. However, there were no changes in behavior or abnormalities observed in the discontinuation phase beyond those that occurred during drug treatment. Upon discontinuation of drug treatment, the CDP group presented with signs of decreased body weight, hunched body position, decrease in body temperature, transient straub tail, and decreased locomotor activity. These data indicate that daridorexant did not produce alterations of the physiological, neurobehavioral, or locomotor parameters during the discontinuation phase of the study. As a result, at the doses tested, there is no indication that daridorexant produces physical dependence and withdrawal.

3. Clinical Pharmacology

Determining the clinical pharmacology of a drug is an important aspect in understanding the mechanism of action of a drug of abuse. Understanding the PK parameters can give an indication as to how a drug will be abused.

3. 1 Absorption, Distribution, Metabolism, Elimination (ADME)

The Applicant conducted 18 phase 1 clinical studies in healthy adults and in special populations to assess the PK and PD of daridorexant. This review will only contain those studies that are relevant to the assessment of the abuse potential of daridorexant, for example, studies conducted in healthy adults and those conducted to assess the abuse potential of the drug at relevant doses.

Study # AC-078-101

This was a single-ascending dose, placebo controlled, double-blind, mass balance, metabolism, and absolute bioavailability study that was conducted to determine the safety and tolerability of

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daridorexant. Forty healthy male subjects were given doses of 5, 25, 50, 100, and 200 mg of daridorexant as two different formulations. Formulation A was a hard gelatinized capsule for oral administration and formulation B was a (b) (4) based formulation with ^{14}C-labled daridorexant to conduct the mass balance study.

The blood samples were collected predose at -2 hours and 0 min, and post dose at 10, 20, 30, 40, 50 and 60 minutes, and 1.5, 2, 2.5, 3, 4, 3.5, 4.5, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, and 96 hours

The PK parameters presented in Table 10 are those of the hard gelatinized capsules and indicate that the highest therapeutic dose of 50 mg produced a C_{max} of 1231.48 ng/mL two hours after oral administration. The total exposure at this dose (AUC0-inf) was 7433.04 ng·h/mL and the half-life was 7.45 h. Notably, the half-life increases with dose and was up to 8.84 hours at an oral dose of 200 mg. In the mass balance part of the study, measurable plasma levels of daridorexant were observed 10 minutes after administration and lasted for up to 72 hours in each of the subjects.

Table 10: Plasma PK Parameters of Single Oral Dose of Daridorexant as a Hard Gelatinized Capsule in Fasted Healthy Subjects (data obtained from NDA 214985, Final study report for study # AC-078-101)

	Dose of Daridorexant (mg)				
PK Parameters	**5**	**25**	**50**	**100**	**200**
C_{max} (ng/mL)	159.67	631.58	1231.48	1556.81	1868.94
T_{max} (h)	0.8	1	2	2.5	2.75
$AUC_{0\text{-}inf}$ (ng·h/mL)	987.3	2716.42	7433.04	12349.62	22970.72
$T_{1/2}$ (h)	6.51	6.1	5.92	7.45	8.84

Study # AC-078-102

This study was a phase 1, single and multiple ascending dose study to investigate the PK, PD, safety, and tolerability of daridorexant in healthy subjects. This study was divided into three parts: Part A included healthy young adults that received multiple oral doses of daridorexant, Part B was designed to administer single oral doses to elderly subjects and Part C administered multiple oral doses to young and elderly subjects in the evening. In order to make a cross-study comparison with the single dose PK data from Table 8, only the PK data gathered for Part A will be discussed in this section. In Part A of the study, multiple oral doses of daridorexant of 10, 25, and 75 mg were administered once daily in the mornings for five days.

The blood samples were collected predose at -2 hours and 0 min, and post dose at 10, 20, 30, 40, 50 and 60 minutes, and 1.5, 2, 2.5, 3, 4, 3.5, 4.5, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, and 96 hours.

Data obtained from the study indicate that subjects reached steady state after three days (data not presented here). The data in Table 11 indicate that there is little to no accumulation of the drug after five days of once daily administration and that increasing doses did not affect the Tmax. Both the AUC and

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the half-life of the drug increased in a linear fashion, even at steady state, and similar to the single dose procedure from Study # AC-078-101.

Table 11: PK Parameters of Daridorexant after Multiple Oral Doses of in Fasted Healthy Subjects (data obtained from NDA 214985, Module 2.7.2, Final study report for study # AC-078-102)

	Dose of Daridorexant (mg)		
PK Parameters	**10**	**25**	**75**
C_{max} (ng/mL)	279.54	615.51	1308.23
T_{max} (h)	1	1	1.07
$AUC_{0\text{-}inf}$ (ng·h/mL)	1688.04	6174.06	17745.73
$T_{1/2}$ (h)	5.6	6.71	8.54

The effect of food, ethanol, and other drugs on the PK parameters of daridorexant was also assessed by the Applicant. In study # ID-078-113 the Applicant determined that administration of 50 mg daridorexant 30 minutes after a high-fat high-calorie meal did not affect the overall exposure of the drug. However, the T_{max} was delayed by 1.3 hours and the C_{max} was decreased by 16%. These data indicate that food is not likely to alter the abuse potential of the drug. In Study ID-078-111 the Applicant tested the coadministration of daridorexant (50 mg oral) and ethanol (5 hours IV at 0.6 g/L) on several PK and PD parameters. Overall, co-administration of ethanol and daridorexant did not alter the PK parameters of daridorexant, however, it did affect several PD parameters which will be discussed in Section 4.

4. Clinical Studies

4.1 Human Abuse Potential Studies

1. Human abuse potential (HAP) study with Daridorexant (Study # ID-078-107)

This HAP study was a Randomized, double-blind, double-dummy, placebo- and active-controlled, 6-way cross-over study to evaluate the abuse potential of single oral doses of Daridorexant. The study consisted of four phases: screening, qualification, treatment, and follow-up.

The primary objective of the study was to determine the abuse potential of daridorexant using placebo as a control and suvorexant and zolpidem as positive controls. The Secondary objectives consisted of assessing the safety and tolerability of daridorexant at therapeutic and supra-therapeutic single doses.

Subjects were healthy male or female adults, 18 to 55 years of age who have used sedatives for recreational purposes at least 10 times in their lives and at least once in the 12 weeks before screening. A total of 72 subjects were randomized to the treatment phase and 63 subjects completed the study.

The inclusion and exclusion criteria were standard and included the following criteria that are of specific interest to an abuse-related study:

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Inclusion criteria included:

- Current recreational drug users who have used sedatives (e.g., benzodiazepines, zolpidem, eszopiclone, gamma-hydroxybutyrate, barbiturates) for recreational purposes at least 10 times in their lives and at leave once in the 12 weeks before screening.

Exclusion criteria included:

- Substance or alcohol dependence (excluding caffeine or nicotine) within the past 2 years as defined by the DSM-IV-TR

- Participation in a substance or alcohol rehabilitation program to treat substance or alcohol dependence

- Heavy smoker (>20 cigarettes per day) and/or unable to abstain from smoking or unable to abstain from the use of prohibited nicotine-containing products for at least 10 hours.

Qualification Phase

The qualification phase was a double-blind cross-over drug discrimination test in which subjects were asked to discriminate between the effects of a single oral dose of 150 mg suvorexant (CIV), 30 mg zolpidem, and placebo. Subjects were dosed on day 1 of the study with each treatment being dosed approximately 3 days apart. Subjects received the study drugs on test days following a fasting period of at least 8 hours. Subjects were required to continue fasting during the test session for at least 4 hours after treatment administration. The qualification criteria consisted of:

1. The ability to distinguish orally administered suvorexant (150 mg) and zolpidem (30 mg) from placebo on the bipolar Drug Liking ('at this moment') visual analog scale (VAS). A Drug Liking score $\geq$ 15 points higher, relative to placebo, on this scale was necessary.

2. Acceptable placebo response based on Drug Liking (score between 40 and 60 points, inclusive).

3. Ability to complete the PD assessments and acceptable overall responses, as judged by the investigator or designee.

4. Able to tolerate doses of positive control drugs as judged by the investigator or designee based on available safety data.

5. General behavior suggested that the subject could successfully complete the study, as judged by the research site staff.

Treatment Phase

The washout period between the last treatment of the Qualification phase and the first treatment of the Treatment phase was three days. Eligible subjects (as determined by the Qualification phase) entered

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the Treatment phase and remained as inpatients in the clinical research unit (CRU). Subjects were randomized to receive each of the six treatments in a randomized, double-blind, double-dummy fashion:

- Placebo
- 50 mg daridorexant
- 100 mg daridorexant
- 150 mg daridorexant
- 30 mg zolpidem
- 150 mg suvorexant

Each subject received five over-encapsulated tablets and three tablets of daridorexant or its matching placebo.

For each treatment, subjects were fasted for at least ten hours predose and for four hours post-dose. Study drug administration in each treatment period was separated by a minimum washout interval of 3-days. Thus, a sufficiently long washout period was used in this study.

The proposed highest therapeutic dose of daridorexant is 50 mg once/day, therefore the Applicant used this dose as their lowest dose and included doses 2- to 3-fold higher as supratherapeutic doses.

Subjective and Cognitive Measures

The T_{max} of zolpidem, suvorexant, and daridorexant is 1 hour after dosing. The assessment times varied depending on the endpoint to be measured, however, they covered the length of the study and PD assessments were conducted at the appropriate times. The pharmacodynamic measures include the use of visual analog scales (VASs), safety endpoints, and observer's assessments, and were conducted at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose. All other assessments for PK were conducted at 0, 0.25 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose.

The primary measure was:

- Drug Liking ('at this moment') VAS Emax (Bipolar) (Emax)

The secondary measures included:

- Drug Liking VAS ("at this moment"), (Emin, TEmax, TEmin, TA_AUE)
- Overall Drug Liking VAS (Emax and Emin)
- Take Drug Again VAS (Emax and Emin)
- High VAS (Emax and Emin)
- Good Drug Effects VAS (Emax, TEmax, TA_AUE)
- Bad Drug Effects VAS (Emax, TEmax, TA_AUE)
- Drug Similarity scale (Emax)
- Drowsiness/Alertness VAS (Emax, Emin, TEmax, TA_AUE)
- Bowdle VAS (Emax) – psychedelic effect
- Any effects VAS (Emax, TEmax, TA_AUE)

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The Applicant also assessed observer-rated measures of sedation and cognitive/psychomotor impairment:

- Observer assessment of alertness/sedation (OAA/S) scale
- Reaction time task (RTT)
    - RTI five-choice error score
- Paired Associates Learning (PAL)
- Rapid visual information processing (RVP)
    - RVP median response latency

Pharmacokinetic Endpoints:

- C_{max}
- T_{max}
- AUC_{0-t}
- Half-life

Safety Endpoints:

- Incidence, frequency, and severity of AEs
- Vital signs (blood pressure, respiratory rate, heart rate, and oral temperature)
- Electrocardiograms (ECGs)
- Clinical laboratory test results (clinical chemistry, hematology, urinalysis)
- Physical examination findings
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Results

The data below were drawn from the Statistical Review and Evaluation of the present HAP study, as conducted by Dr. Ling Chen, FDA Office of Biostatistics VI. The primary measure of Drug Liking ('at this moment'), as well as the secondary measures Take Drug Again and Overall Drug Liking in response to zolpidem, suvorexant, daridorexant, and placebo were evaluated for statistically significant differences by Dr. Chen as well as the Applicant.

Subjects in the qualification phase had a maximum mean drug liking (bipolar VAS, Emax) score of 84.7 ± 1.38 for suvorexant, 82.9 ± 1.3 for zolpidem, and 50.2 ± 0.1 for placebo. The mean difference in these scores between drug treatment and placebo is 34.6 ± 1.4 for suvorexant and 32.7 ± 1.4 for zolpidem indicating that subjects were able to discriminate between drug treatment and placebo and move to the treatment phase of the study. However, the drug treatment scores are higher than those presented in Table 12 which is data gathered from a modified completer population (MCP). The MCP is defined as completers who do not satisfy the following criteria for the primary endpoint, Drug Liking (Emax).

1. The difference between maximum and minimum of Emax scores for all treatments is smaller than or equal to 5 (that is, similar Emax scores across all treatments including placebo).

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2. $Emax\ (P) > 60$ and $Emax(P) - Emax(Z30) \geq 5$ (or $Emax(P) - Emax(S150) \geq 5$).

This analysis removed five subjects from the completer population (Subject numbers (b) (6)) generating a MCP that contains 58 subjects compared to the N=63 analyzed by the Applicant. Importantly, this change to the completer population did not change the statistical outcome, between the Applicant and the Agency, of the primary or secondary measures analyzed in Table 12.

The subjective measures of Drug Liking, Take Drug Again, and Overall Drug Liking are bipolar scales ranging from 0-100 with 50 as neutral, and an a priori defined acceptable placebo range of 40-60.

The data in Table 12 indicate that the positive comparators, suvorexant and zolpidem, were significantly different from placebo for the primary measure of Drug Liking, validating the study. The positive comparators were also significantly different from placebo in the secondary measures of Take Drug Again and Overall Drug Liking. Also, doses of 100 and 150 mg daridorexant did not produce less drug liking than the positive comparators and this was repeated in the secondary measures of Take Drug again and Overall Drug Liking. However, the lower dose of 50 mg daridorexant was significantly different from the positive comparators in the primary measure of Drug Liking. The 50 mg dose of daridorexant was significantly different from placebo in the secondary measure of Overall Drug Liking. Taken together, these data indicate that the abuse potential of daridorexant is not significantly different from zolpidem and suvorexant.

Table 12: Effects of Oral Placebo, Zolpidem 30 mg, Suvorexant 150 mg, and Daridorexant (50, 100, and 150 mg) on Key Subjective Measures (VAS) - Emax Scores (scale 0-100, mean ± SD) Using the Modified Completer Population

	Placebo	**Zolpidem 30 mg**	**Suvorexant 150 mg**	**Daridorexant 50 mg**	**Daridorexant 100 mg**	**Daridorexant 150 mg**
Drug Liking[A] (at this moment) (bipolar) (N=58)	52.8 ± 1.2	80.1 ± 1.9*	80.3 ± 2.0*	72.0 ± 2.2*[ZS]	79.1 ± 2.2	80.6 ± 1.9
Take Drug Again[A] (bipolar) (N=58)	53.4 ± 1.8	79.8 ± 2.3*	81.6 ± 2.3*	74.3 ± 2.9	79.5 ± 2.5	81.7 ± 2.4
Overall Drug Liking[A] (bipolar) (N=58)	53.8 ± 1.4	78.6 ± 2.3*	81.3 ± 2.2*	73.1 ± 2.6*	79.2 ± 2.5	80.6 ± 2.3

[A] data based on a modified completer population: subjects (b) (6) were removed from the analysis
* = significantly different from placebo with a p-value < 0.0001
[Z] = significantly different from zolpidem (30 mg) with a p-value < 0.0001
[S] = significantly different from suvorexant (150 mg) with a p-value < 0.0001

The Applicant also assessed several other secondary measures. The measures Good Drug Effects, High, and Bad Drug Effects are unipolar scales ranging from 0-100 with 0 as neutral and an acceptable placebo range of 0-20. The measures of Good Drug Effects and High were close to neutral for the placebo group while all of the other treatment groups were significantly higher (Table 13). Similar to the primary measure (i.e., Drug Liking), the 50 mg daridorexant treatment was significantly lower than the positive controls and the 100 and 150 mg treatments were not significantly different from the positive

comparators. The measurement of Bad Drug effects was statistically significantly different between the drug treatment groups and placebo, however, the overall magnitude of the responses is very low and it is unclear whether this would be a significant effect in an abuse setting. The results for Any Effects and Alertness/Drowsiness scales presented in Table 13 are indicative of the therapeutic indication of the drugs used in the study (e.g., insomnia) and indicate that all of the drugs produce sedative effects compared to placebo. The Applicant also measured the internal and external perceptions of psychedelic effects of daridorexant using a Bowdle VAS. The positive comparators and all doses of daridorexant produced statistically higher perceptions of psychedelic effects compared to placebo.

Table 13: Mean of Secondary Endpoints Zolpidem 30 mg, Suvorexant 150 mg, and Daridorexant (50, 100, and 150 mg)

	Placebo	**Zolpidem 30 mg**	**Suvorexant 150 mg**	**Daridorexant 50 mg**	**Daridorexant 100 mg**	**Daridorexant 150 mg**
High (unipolar) (N=63)	5.5 ± 16.6	60.2 ± 32.6*	50.1 ± 37.1*	38.2 ± 36.2*^{ZS}	48.4 ± 38.2*	58.1 ± 35.0*
Good Drug Effects (unipolar) (N=63)	7.7 ± 19.3	60.4 ± 29.4*	63.1 ± 31.7*	45.0 ± 34.2*^{ZS}	59.0 ± 33.1*	65.4 ± 28.3*
Bad Drug Effects (unipolar) (N=63)	1.1 ± 5.2	14.0 ± 27.6*	11.8 ± 23.3*	3.5 ± 12.9	10.7 ± 23.7*	10.5 ± 20.9*
Any Drug Effects (unipolar) (N=63)	7.8 ± 19.4	62.9 ± 27.5*	70.9 ± 29.1*	47.2 ± 34.3*^{ZS}	62.0 ± 32.2*	68.5 ± 26.1*
Alertness/Drowsiness (Emin) (unipolar) (N=63)	42.1 ± 15.8	19.4 ± 15.2*	12.1 ± 12.2*	23.3 ± 17.8*^{ZS}	13.9 ± 14.2*	9.3 ± 10.4*

* = significantly different from placebo with a p-value < 0.0001
^{Z} = significantly different from zolpidem (30 mg) with a p-value < 0.0001
^{S} = significantly different from suvorexant (150 mg) with a p-value < 0.0001

The Applicant also conducted a Drug Similarity VAS 12-hours post-dosing. This VAS is a 0-100 scale where 0 equals definitely not and 100 equals definitely so in regard to comparison of the following drugs: amphetamine, barbiturates, benzodiazepines, cannabis, cocaine, ecstasy, ketamine, lysergic acid diethylamide, methamphetamine, opioids, phencyclidine, psilocybin, and sedatives. The data are presented in the review conducted by Dr. Ling Chen. In brief, the subjects found daridorexant to be most similar to sedatives (mean range: 43.3 to 83.3) and ketamine (CIII) (mean range: 66.0 to 75.0).

Adverse Events in Core Phase

The Applicant monitored for treatment emergent AEs across all arms of the Treatment phase of the study. All AEs, including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The abuse related AEs are summarized in Table 14 and indicate that supratherapeutic doses of daridorexant (i.e., 100 and 150 mg) produce a similar number and percent of AEs to the positive comparator drugs. A notable difference being the reports of Euphoric Mood which were lower in the daridorexant treatment arms compared to the positive comparators.

Reference ID: 4866112

Table 14: Abuse Related Treatment Emergent Adverse Events Reported During the Treatment Phase of HAP Study # ID-078-107, expressed as N (%).

Drug	**Daridorexant (mg)**			**Suvorexant (mg)**	**Zolpidem (mg)**	**Placebo**
Preferred Term	**50 (N=67)**	**100 (N=69)**	**150 (N=67)**	**150 (N=67)**	**30 (N=69)**	**0 (N=66)**
Abnormal Dreams	1 (1.5)	1 (1.4)	--	2 (3.0)	--	--
Affect Lability	--	--	--	--	1 (1.4)	--
Confusional State	1 (1.5)	--	1 (1.5)	--	8 (11.6)	--
Disturbance in Attention	1 (1.5)	--	--	--	2 (2.9)	--
Dizziness	1 (1.5)	2 (2.9)	1 (1.5)	1 (1.5)	4 (5.8)	1 (1.5)
Euphoric Mood	2 (3.0)	4 (5.8)	3 (4.5)	6 (9.0)	14 (20.3)	1 (1.5)
Fatigue	2 (3.0)	3 (4.3)	4 (6.0)	2 (3.0)	2 (2.9)	--
Feeling Abnormal	1 (1.5)	1 (1.4)	1 (1.5)	3 (4.5)	10 (14.5)	--
Feeling Drunk	--	--	1 (1.5)	--	--	--
Hallucination, Visual	--	--	--	1 (1.5)	--	--
Illusion	--	--	1 (1.5)	--	2 (2.9)	--
Mental Impairment	--	--	--	--	2 (2.9)	--
Paresthesia	--	--	1 (1.5)	1 (1.5)	1 (1.4)	--
Somnolence	33 (58.2)	46 (79.7)	59 (88.1)	56 (83.6)	64 (92.8)	16 (24.2)

Pharmacokinetics

The majority of the peak PD effects produced by daridorexant were present within 1 to 2 hours of oral administration of the drug. These data are supported by the Tmax of the drug which is 1.1 hour. The duration of the PD effects was longer for suvorexant because of the longer half-life but was similar for zolpidem and daridorexant lasting six to eight hours post-dose.

Table 15: PK Parameters of a Single Oral Doses of Daridorexant at 50, 100, and 150 mg in HAP Study # ID-078-107

	Dose of Daridorexant (mg)		
PK Parameters	**50**	**100**	**150**
C_{max} (ng/mL)	1115.1	1653.4	1958.4
T_{max} (h)	1.1	1.1	1.1
$AUC_{0\text{-}inf}$ (ng·h/mL)	7692.4	13847.6	18983.2
$T_{1/2}$ (h)	7.2	8.4	8.6

Conclusion

The data from HAP study # ID-078-107 indicate that the abuse potential of daridorexant is similar to that of zolpidem and suvorexant, both of which are controlled in schedule IV of the CSA. The data from the study indicate that the 50 mg dose of suvorexant produced significantly lower PD measures compared to the positive comparators, however, they were significantly greater than placebo. Notably, the 50 mg dose is the highest therapeutic dose of daridorexant, and it was compared to doses of the positive comparators, 30 mg zolpidem and 150 mg suvorexant, that are supratherapeutic doses which are 3-fold and 7.5-fold the highest therapeutic dose approved by FDA. The supratherapeutic doses of 100 and 150 mg (2- to 3-fold the highest proposed therapeutic dose) produced PD measures that were not significantly different from those of the positive comparators used in this study. As a result, Study # ID-078-107 is supportive evidence that daridorexant has abuse potential similar to the schedule IV drugs zolpidem and suvorexant.

4.2 Adverse Event Profile Through all Phases of Development

Adverse Events in Clinical Studies Conducted by the Applicant

The Applicant conducted 18 phase 1 studies to assess the safety, pharmacokinetics, and bioavailability of daridorexant. All AEs, including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description and analysis of abuse-related AEs found during these studies.

Table 16: Studies Completed by the Applicant and Included in the Evaluation of Abuse-Related Adverse Events

Study	Subjects completed	Dose of Daridorexant (mg)
AC-078-101	Healthy/40	5, 25, 50, 100, 200
AC-078-102-A	Healthy/31	10, 25, 75
AC-078-102-B	Healthy/27	5, 15, 25
AC-078-103	Healthy/13	25
AC-078-104	Healthy/20	25
AC-078-105	Healthy/41	25, 50
AC-078-106	Healthy/20	25
ID-078-107	Healthy/68	50, 100, 150
AC-078-108	Healthy/60	50, 100
AC-078-109/-110	COPD or OSE/56	50
AC-078-111	Healthy/22	50
AC-078-112	Hepatic imp./24	25
AC-078-113	Healthy/20	50 + ethanol
AC-078-114	Healthy/24	50
AC-078-115	Renal imp./15	25
AC-078-116	Healthy/48	10, 25, 50
AC-078-117	Healthy/36	50, 200
AC-078-120	Healthy/24	50

Phase 1 Studies

Reference ID: 4866112

The data presented below (Table 17) are composed of the Phase 1 studies in which healthy adult subjects received oral doses of daridorexant ranging from 5 mg to 200 mg. The AEs were compiled from the studies listed in Table 16 excluding the HAP study (ID-078-107), which is presented in Table 14, and Study # ID-078-111 which is a combination study conducted with ethanol (EtOH) and is presented in Table 19.

The data indicate that a total of 10 preferred terms possibly indicative of abuse were reported in the phase 1 studies out of a total of 478 subjects who received drug treatment. Somnolence (252 (52.7%)) was reported at every dose at a rate that is 2- to 3-fold higher than that reported in the placebo (21 (31.4%)) treated group. The Applicant states the high number of reports of Somnolence are expected, given the intended indication (insomnia), however, the data clearly indicate that daridorexant increased the reports of this AE above placebo. The second and third most reported AEs were Fatigue (52 (10.9)) and Disturbances in Attention (18 (3.8)) with all other AEs being reported at less than 2% of the study population (Table 18). It should be noted, that there were 3 (13%) reports of Euphoric Mood in study # ID-078-114, however, these reports were from subjects that received single oral doses of daridorexant (50 mg) + citalopram (20 mg). It is unclear why these subjects reported this preferred term and if this drug combination may be producing a euphoric effect.

Table 17: Abuse Related Treatment Emergent Adverse Events Reported in Phase 1 Studies by Dose (excluding study # ID-078-107 and Study # ID-078-111 from Table 16) expressed as N (%)

	Daridorexant Dose (mg)								
Preferred Term	**5 N=6**	**10 N=20**	**15 N=6**	**25 N=172**	**50 N=195**	**75 N=8**	**100 N=65**	**200 N=6**	**Placebo N=156**
Anger	--	1 (5.0)	--	--		--	--	--	--
Bradyphrenia	--	--	--	--	1 (0.5)	--	--	--	--
Disturbance in attention	1 (16.7)	--	--	6 (3.5)	9 (4.6)	--	--	2 (33.3)	--
Dizziness	1 (16.7)	1 (5.0)	--	2 (1.2)	3 (1.5)	--	1 (1.5)	--	5 (3.2)
Fatigue	--	--	--	12 (7.0)	22 (11.3)	2 (25.0)	15 (23.1)	1 (16.7)	3 (1.9)
Feeling abnormal	--	--	--	1 (0.6)	--	--	--	--	--
Feeling of relaxation	--	1 (5.0)	--	--	--	--	--	--	--
Hangover	--	--	--	--	2 (1.0)	--	--	--	1 (0.6)
Nervousness	--	--	1 (16.7)	--		--	--	--	--
Somnolence	5 (83.3)	7 (35.0)	2 (33.3)	97 (56.4)	96 (49.2)	6 (75.0)	34 (52.3)	5 (83.3)	21 (31.4)

Table 18: Total Abuse Related Treatment Emergent Adverse Events Reported in Phase 1 Studies (excluding study # ID-078-107 and Study # ID-078-111 from Table 16) expressed as N (%)

Preferred Term	**N (%)**
Anger	1 (0.2)

Bradyphrenia	1 (0.2)
Disturbance in attention	18 (3.8)
Dizziness	8 (1.8)
Fatigue	52 (10.9)
Feeling abnormal	1 (0.2)
Feeling of relaxation	1 (0.2)
Hangover	2 (0.4)
Nervousness	1 (0.2)
Somnolence	252 (52.7)

The Applicant also conducted a study to determine the effects of taking daridorexant in combination with ethanol. In this cross-over study, subjects were divided into one of four treatment groups:

A. Daridorexant (50 mg) + EtOH
B. Daridorexant (50 mg) + placebo
C. Daridorexant placebo + EtOH
D. Daridorexant placebo + placebo

The abuse-related AEs reported in this study indicate that the major difference between subjects who received daridorexant (Group B) alone versus those who received daridorexant + EtOH (Group A) was that Group A felt drunk as well as having all of the daridorexant alone related AEs. The data suggest that daridorexant should not be consumed with ethanol. Appropriate warnings on this concomitant use should be addressed in the drug's label.

Table 19: Abuse-Related Treatment Emergent Adverse Events Reported in Subjects Administered Daridorexant + Ethanol, Study # ID-078-111, data expressed as N (%)

Preferred Term	**A**	**B**	**C**	**D**
Disturbance in Attention	1 (4.8)	2 (9.5)	--	--
Dizziness	4 (19.0)	2 (9.50	4 (19.0)	--
Fatigue	3 (14.3)	3 (14.3)	3 (14.3)	1 (4.8)
Feeling Drunk	4 (19.0)	--	5 (23.8)	--
Somnolence	14 (66.7)	15 (71.4)	7 (33.3)	5 (23.8)

A – 50 mg daridorexant + EtOH
B – 50 mg daridorexant + placebo
C – Daridorexant placebo + EtOH
D – Daridorexant placebo + placebo

Phase 2 Studies

Two phase 2 studies were conducted to evaluate the efficacy and safety of daridorexant in subjects with insomnia disorder. Study AC-078A201 was conducted in adult subjects, aged 18 to 64 years inclusive, and Study AC-078A202 was conducted in elderly subjects, aged ≥ 65 years.

Reference ID: 4866112

Study # AC-078A201 was conducted to evaluate the dose-response of daridorexant on sleep parameters and to assess its safety and tolerability to systemic exposure. The drug was administered as hard gelatin capsules as once daily oral doses of 5, 10, 25, and 50 mg to adult subjects with insomnia disorder according to DSM-5 criteria. In the study, 239 subjects received daridorexant, 60 received zolpidem, and 60 received placebo.

Study # AC-078A202 was conducted to evaluate the dose-response of daridorexant on sleep parameters and to assess its safety and tolerability to systemic exposure. The drug was administered as tablets as once daily oral doses of 10, 25, and 50 mg to adult Japanese subjects (N = 58) with insomnia disorder according to DSM-5 criteria.

The AEs from the two phase 2 studies were compiled and are presented in Table 20. Similar to the previous data, the reports of Somnolence exceed reports of other preferred terms that may be associated with abuse potential. In these studies, the percent reports of Somnolence (14 (5.86%)) were similar to that of Zolpidem (3 (5%)) and Placebo (3 (5%)).

Table 20: Abuse-Related Treatment Emergent Adverse Events Reported in Phase 2 Studies, Data Expressed as N (%)

Preferred Term	**Daridorexant (N=239)**	**Zolpidem (10 mg) (N=60)**	**Placebo (N=60)**
Anxiety	--	1 (1.67)	--
Balance Disorder	1 (0.42)	--	--
Dizziness	3 (1.26)	4 (6.67)	1 (1.67)
Fatigue	5 (2.09)	4 (6.67)	2 (3.33)
Feeling Abnormal	--	--	--
Hallucination, visual	--	--	1 (1.67)
Nervousness	1 (0.42)	--	--
Somnolence	14 (5.86)	3 (5.00)	3 (5.00)

Phase 3 Studies

Three Phase 3 studies were conducted, as confirmatory studies, in adult and elderly subjects with insomnia disorder. They were similar in Design to the Phase 2 studies and used doses of 25 and 50 mg (Study # ID-078A301) and 10 and 25 mg (Study # ID-078A302 and Study # ID-078A303). The studies consisted of a 21- to 30-day screening phase, followed by a 13- to 24- days placebo phase, followed by a 12-week treatment phase. The end of the study consisted of a 1-week placebo run-out period for safety and follow-up. After these studies were conducted subjects were offered enrollment in study # ID-078A303 which was a long-term treatment safety and efficacy study in which subjects remain on drug treatment for one year (this study is ongoing). The AEs for these studies are compiled into Table 21. Similar to the Phase 1 and Phase 2 studies, the highest number of reports comes from somnolence (38 (2.14%), fatigue (34 (1.91%)), and dizziness (26 (1.46%)). The placebo group also reported higher levels of these AEs suggesting that these AEs may be a symptom of insomnia, however, the reports from the drug treatment groups are 2- to 3- fold that of the placebo group. This demonstrates that the drug either produces or worsens these sensations in the insomnia population. In regards to abuse, these AEs

are typically not a concern unless they are reported with AEs more indicative of abuse (i.e., euphoria, hallucinations).

The only reports of AEs indicative of abuse in the phase 3 studies were those related to hallucinations. All cases of hallucinations were believed to be the result of the study treatment, however, they resolved without further treatment and three of the four subjects completed the study. The fourth subject, who did not complete the study, was removed from the study for a multitude of health reasons.

1. In Study ID-078A301, subject number (b) (6) was a 25-year-old Caucasian female with insomnia disorder. On day nine of the study the subject reported visual hallucinations when falling asleep and throughout the night while taking 25 mg of daridorexant. No action was taken to change treatment and the subject completed they study with 100% treatment compliance.

2. In Study ID-078A302, subject number (b) (6) was a 55-year-old Caucasian female with insomnia disorder. On day 3 of the study the subject unintentionally took two tablets (50 mg) of the test drug and experienced sleep paralysis and mixed hallucinations. The subject was prematurely discontinued from the study as a result of the overdose and AEs which were both resolved without intervention.

3. In Study ID-078A302, subject number (b) (6) was a 46-year-old African American female with insomnia disorder. On day 34 of the study the subject experience hypnagogic hallucination, sleep paralysis, and periodic limp movement disorder. No treatment was given, and the AEs resolved the following day. The subject completed the study as designed with 100% drug compliance.

4. In Study ID-078A302, subject number (b) (6) was a 66-year-old Asian female with insomnia disorder. The onset and stop date are unknown because the AE is based on later questioning of the subject. No treatment was given. The subject completed the study as designed with 100% drug compliance

Table 21: Abuse-Related Treatment Emergent Adverse Events Reported in Phase 3 Studies, Data Expressed as N (%)

Preferred Term	**Daridorexant (N=1779)**	**Placebo (N=743)**
Accidental Overdose	29 (1.63)	6 (0.81)
Confusional State	3 (0.17)	--
Depressed Mood	5 (0.28)	--
Disturbance in Attention	7 (0.39)	--
Dizziness	26 (1.46)	6 (0.81)
Fatigue	34 (1.91)	6 (0.81)
Feeling Abnormal	2 (0.11)	2 (0.27)
Hallucination, Visual	1 (0.06)	--
Hallucinations, mixed	1 (0.06)	--

Hangover	5 (0.28)	--
Hypnagogic Hallucination	2 (0.11)	--
Irritability	2 (0.11)	3 (0.40)
Mood Altered	--	1 (0.13)
Overdose	6 (0.34)	--
Somnolence	38 (2.14)	10 (1.35)

Conclusion

The abuse-related adverse event profile of daridorexant across all phases of clinical development indicate that the most common treatment emergent AEs were somnolence, fatigue, and dizziness. These AEs are typically not strong indicators of abuse potential when reported without AEs such as euphoria and hallucinations. These AEs are also prevalent in the insomnia population in which the drug was studied, however, the rate of reports was prevalent in healthy populations as well. Four reports of hallucinations were indicated in the Phase 3 studies all of which resolved with no intervention. It is unclear if the hallucinations were the direct result of the study drug or perceptual changes elicited by a sleep state brought on by the drug. Finally, the HAP study and the Phase 2 studies indicate that daridorexant produces a similar AE profile as that of other sleep-inducing drugs such as the positive comparators zolpidem and suvorexant. There were no signs of physical dependence or symptoms of withdrawal upon cessation of drug treatment at the end of the phase 3 studies.

4.4 Evidence of Abuse, Misuse, and Diversion in Clinical Trials

There were no reports of misuse, abuse, or diversion of daridorexant in clinical trials. There were several reports of overdose and noncompliance, however, these were the result of subjects mistakenly taking two tablets instead of one during the study.

5. Regulatory Issues and Assessment

The Applicant proposes to control daridorexant in Schedule V of the CSA based on their analysis of the in vitro, in vivo, and clinical trial data. The data provided by the Applicant are very similar to other orexin antagonists such as suvorexant and lemborexant which are currently controlled in schedule IV of the CSA. There does not appear to be a significant difference in the abuse potential or ability to produce physical dependence between daridorexant and other approved orexin receptor antagonists controlled in schedule IV of the CSA (i.e., suvorexant and lemborexant).

Based on the totality of the data provided, CSS recommends that suvorexant be controlled in schedule IV of the CSA.

References

Reference ID: 4866112

Balster RL and Bigelow GE (2003) Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug Alcohol Depend* **70**:S13-40.

Doat MM, Rabin RA and Winter JC (2003) Characterization of the discriminative stimulus properties of centrally administered (-)-DOM and LSD. *Pharmacol Biochem Behav* **74**:713-721.

Sannerud CA and Ator NA (1995) Drug discrimination analysis of midazolam under a three-lever procedure. II: Differential effects of benzodiazepine receptor agonists. *J Pharmacol Exp Ther* **275**:183-193.

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Division of Pediatrics and Maternal Health Review

Date: 7/8/2021 **Date consulted:** 2/2/2021

From: Kristie Baisden, DO, Medical Officer, Maternal Health
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To: Latrice Wilson, Regulatory Project Manager (RPM)
Division of Psychiatry (DP)

Drug: Quviviq (daridorexant)

NDA: 214985

Applicant: Idorsia Pharmaceuticals, Ltd.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Treatment of adult patients with insomnia (b) (4) (b) (4).

Materials Reviewed:

- NDA 214985 submitted on January 8, 2021.
- DPMH consult review of Rozerem (ramelteon) NDA 021782, Catherine Roca, MD, November 21, 2018. DARRTS Reference ID 4353055.[1]

[1] The Rozerem, Belsomra, and Dayvigo NDA reviews were part of the materials reviewed but were not a source relied upon for the labeling recommendations below. Rather the cross-reference is included to avoid duplicating background information relevant to this class of products.

Reference ID: 4823307

- DPMH consult review of Belsomra (suvorexant) NDA 204569, Catherine Roca, MD, October 15, 2019. DARRTS Reference ID 4506225.[1]
- DPMH consult review of Dayvigo (lemborexant) NDA 212028, Carrie Ceresa, PharmD, MPH, August 5, 2019. DARRTS Reference ID 4472552.[1]

Consult Question: "DP is requesting DPMH to review labeling and provide input as needed throughout the review cycle."

INTRODUCTION

On January 8, 2021, Idorsia Pharmaceuticals, Ltd. submitted an original NDA (214985) for Quviviq (daridorexant) for the treatment of adult patients with insomnia (b) (4) . On February 2, 2021, the Division of Psychiatry (DP) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections.

BACKGROUND

Drug Characteristics

- *Mechanism of action:* an orexin receptor antagonist
- *Dosage and administration:* 50 mg once per night, taken orally within 30 minutes before going to bed.
- *Molecular weight:* 487.38 g/mol
- *Bioavailability:* 62%
- *Protein binding:* 99.7%
- *Half-life:* 8 hours

Identified safety concerns (based on currently proposed labeling)

- *Contraindications:* narcolepsy
- *Warnings and Precautions:* CNS-depressant effects; sleep paralysis, hallucinations, and cataplexy-like symptoms; worsening of depression/suicidal ideation
- *Adverse reactions:* headache, somnolence, dizziness, fatigue, nausea

Condition: Insomnia and Pregnancy

- Women are 1.5 times more likely to have insomnia than men.[2]
- Sleep disturbances, including insomnia, affect approximately 66-94% of pregnant women. The prevalence of insomnia increases to 73.5% in the third trimester.[3]
- Behavioral modification and pharmacological medications are both used to treat insomnia during pregnancy.
    - Nonpharmacological treatment includes avoiding naps and caffeine, establishing a regular sleep-wake cycle, and minimizing fluid intake close to bedtime.
    - Approximately 4% of pregnant women admit to using some type of pharmacologic sleep aid during pregnancy.[4] Gamma-aminobutyric acid (GABA)

[2] Suh S, Cho N, Zhang J. Sex differences in insomnia: from epidemiology and etiology to intervention. Curr Psychiatry Rep. 2018. 20(9):69.
[3] Reichner C, et al. Insomnia and sleep deficiency in pregnancy. Obstetric Medicine. 2015;8(4):168-171.
[4] Pien GW and Schwab RJ. Sleep disorders during pregnancy. Sleep. 2004;27(7):1405-1417.

Reference ID: 4823307

receptor agonists, such as zaleplon, zolpidem, and eszopiclone, are the most commonly prescribed medications for insomnia during pregnancy.[5]

- Sleep disturbance during pregnancy has been associated with adverse pregnancy outcomes including prenatal depression, gestational diabetes, pre-eclampsia, abnormal length of labor, cesarean section delivery, preterm birth and altered fetal growth.[6]

REVIEW

PREGNANCY

Nonclinical Experience

In animal reproduction studies, oral administration of daridorexant to pregnant rats and rabbits during the period of organogenesis did not cause significant fetal toxicity at doses up to 8 and 10 times the maximum recommended human dose (MRHD) of 50 mg, based on AUC. In the rabbit, daridorexant caused maternal toxicity of decreased weight gain and food consumption at 10 times the MRHD based on AUC. The no observed adverse effect levels (NOAELs) for maternal toxicity are approximately 8 and 4 times the MRHD, based on AUC in the rat and rabbit, respectively. Oral administration of daridorexant to pregnant and lactating rats did not cause significant maternal or developmental toxicity at doses up to 9 times the MRHD, based on AUC. For additional details, refer to the Nonclinical Review by Jia Yao, PhD.

Clinical Trials

Pregnant women were excluded from clinical trials during the development program for daridorexant. The applicant stated no pregnancy exposure cases were reported.

Review of Literature

Applicant's Review of Literature

The applicant did not perform a literature search related to daridorexant use and pregnancy.

DPMH Review of Literature

This Reviewer performed a search in PubMed, Embase, Micromedex[7], TERIS[8], Reprotox[9], and Briggs[10] to find relevant articles related to the use of daridorexant during pregnancy. Search terms included "daridorexant" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." No relevant articles were identified.

LACTATION

Nonclinical Experience

Dariodorexant and its metabolites were present in the milk of lactating rats. For additional details, refer to the Nonclinical Review by Jia Yao, PhD.

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[5] Okun M, et al. A review of sleep-promoting medications used in pregnancy. American Journal of Obstetrics and Gynecology; 428-439. 2015.

[6] Palagini L, et al. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep Medicine. 2014;15:853-859.

[7] Truven Health Analytics information, http://www micromedexsolutions.com/Accessed 6/8/21.

[8] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 6/8/21.

[9] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 6/8/21.

[10] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

Reference ID: 4823307

Clinical Trials
Lactating women were excluded from clinical trials during the development program for daridorexant. The applicant stated no lactation exposure cases were reported.

Review of Literature
Applicant's Review of Literature
The applicant did not perform a literature searched related to daridorexant use and lactation.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, Micromedex[7], TERIS[8], Reprotox[9], and Briggs[10], *Medications and Mothers' Milk*[11], and LactMed[12] to find relevant articles related to the use of daridorexant during lactation. Search terms included "daridorexant" AND "breastfeeding" or "lactation." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Daridorexant was orally administered to female rats at doses of 30, 100, and 300 mg/kg/day prior to and throughout mating and continuing to gestation Day 6. These doses are approximately 0.5, 3, and 9 times the MRHD of 50 mg, based on AUC. Daridorexant increased pre-implantation loss and decreased implantation sites without affecting mating and fertility at 300 mg/kg/day. The NOAEL for female fertility is 100 mg/kg/day, which is approximately 3 times the MRHD of 50 mg, based on AUC.

Daridorexant did not affect fertility when orally administered to male rats at doses of 50, 150, and 450 mg/kg/day prior to and throughout mating. These doses are approximately 1, 3, and 7 times the MRHD of 50 mg, based on AUC.

For additional details, refer to the Nonclinical Review by Jia Yao, PhD.

Review of Literature
Applicant's Review of Literature
The applicant did not perform a literature search related to daridorexant use and fertility.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, Reprotox[9] to find relevant articles related to the use of daridorexant and effects on fertility. Search terms included "daridorexant" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant articles were identified.

[11] Hale, Thomas (2020) Medications and Mothers' Milk online. Accessed 6/8/21.
[12] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 6/8/21.

DISCUSSION AND CONCLUSIONS

Pregnancy

Pregnant women were excluded from clinical trials with daridorexant and no pregnancy exposure cases have been reported. Animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. DPMH recommends subsection 8.1 include a statement that there are no available data on Quviviq use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Daridorexant is indicated for a condition that would be expected to be seen in females of reproductive potential and during pregnancy. Therefore, DPMH recommends a postmarketing requirement (PMR) for the applicant to conduct a pregnancy exposure registry and a complimentary study of a different design. DPMH also recommends that language regarding the pregnancy exposure registry is included in subsection 8.1 and section 17 of labeling.

Lactation

Lactating women were excluded from clinical trials with daridorexant and no lactation exposure cases have been reported. There are no available data on the presence of daridorexant in human milk, the effects on the breastfed infant, or the effects on milk production. Daridorexant and its metabolites are present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

DPMH recommends subsection 8.2 include a statement consistent with labeling for other drugs in class that infants exposed to Quviviq through breastmilk should be monitored for excess sedation. The following risk/benefit statement should also be included: “the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Quviviq and any potential adverse effects on the breastfed infant from Quviviq or from the underlying maternal condition.”

Daridorexant is indicated for a condition that would be expected to be seen in females of reproductive potential and during lactation. The drug is present in animal milk and given the drug’s characteristics (such as molecular weight less than 800 Daltons), it is possible that the drug will also be present in human milk. Therefore, DPMH recommends a PMR for the applicant to conduct a clinical lactation study.

Females and Males of Reproductive Potential

There are no available human data on the effects of daridorexant on male or female fertility. Animal fertility studies do not indicate any adverse effects. In addition, animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. Therefore, DPMH recommends omitting subsection 8.3 from labeling for Quviviq.

PMR RECOMMENDATIONS

DPMH recommends the following:

1) The applicant should be required to conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to daridorexant during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will assessed through at least the first year of life.
2) The applicant should be required to conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to daridorexant during pregnancy compared to an unexposed control population.
3) The applicant should be required to perform a lactation study using a validated assay in women who have received daridorexant.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and section 17 of labeling for compliance with the PLLR (see below). The labeling recommendations below are pending final input from the Nonclinical Team. DPMH refers to the final NDA action for final labeling.

DPMH Proposed QUVIVIQ (daridorexant) Pregnancy and Lactation Labeling

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KRISTIE W BAISDEN
07/08/2021 03:48:57 PM

TAMARA N JOHNSON
07/08/2021 04:24:34 PM

LYNNE P YAO
07/12/2021 01:00:50 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-214985
Submission Number	001
Submission Date	1/8/2021
Date Consult Received	1/19/2021
Drug Name	Daridorexant
Indication	The treatment of adult patients with insomnia [redacted (b) (4)].
Therapeutic dose	50 mg once daily
Clinical Division	DP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 1/19/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 08/12/2019 in DARRTS (link);
- Sponsor's proposed product label (SN0001; link);
- Sponsor's clinical study protocol # ID-078-117 (SN0001; link);
- Sponsor's clinical study report # ID-078-117 (SN0001; link);
- Sponsor's statistical analysis plan # ID-078-117 (SN0001; link);
- Investigator's brochure Ver 7.0 under IND-128789 (SN0102); and
- Highlights of clinical pharmacology and cardiac safety (SN0005; link).

1 SUMMARY

No significant QTc prolongation effect of daridorexant was detected in this QT assessment.

The effect of daridorexant was evaluated in a thorough QT study (Study # ACT-541468). This is a phase 1, single-center, randomized, double-blind, placebo- and positive-controlled study. The highest dose evaluated was 200 mg, which covers the high clinical exposure scenario (CYP3A inhibition and hepatic impairment, Section 3.1). The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that daridorexant is associated with significant QTc prolonging effect (refer to Section 4.5) – see Table 1 for overall results.

Although the sponsor's by-time moxifloxacin analysis results deviated from the historic moxifloxacin profile, the FDA reviewer performed QT bias analysis and no significant bias was observed. The findings of this analysis are further supported by the available nonclinical data (Sections 3.1.2) and by-time analysis (Section 4.3) and categorical analysis (Section 4.4).

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Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentrations (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Daridorexant 50 mg	748.9	0.8	(-0.3 to 1.9)
QTc	Daridorexant 200 mg	1,809.2	0.5	(-1.8 to 2.9)

For further details on the FDA analysis, please see Section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At a dose 4 times the maximum recommended dose, (b) (4) QUVIVIQ (b) (4) does not prolong the QTc interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Idorsia Pharmaceuticals Ltd. is developing daridorexant for the treatment of insomnia ((b) (4)) in adult patients. Daridorexant (ACT-541468, hydrochloride salt; MW: 487.38 g/mol) is a dual orexin receptor antagonist (acting on both orexin 1 and orexin 2 receptors; equipotent). The orexin neuropeptides (orexin A and orexin B) are believed to act on orexin receptors to promote wakefulness.

The product is formulated as immediate-release film-coated tablet formulation (QUVIVIQ) containing 25 or 50 mg daridorexant (as hydrochloride salt) for oral

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administration. The sponsor also utilized immediate-release capsule formulation during the development. The maximum proposed therapeutic dose is 50 mg once daily (within 30 minutes before going to bed). The peak concentrations of ~1050 ng/mL (Tmax: ~1.5 h; half-life: ~8 h) are observed with the proposed therapeutic dose (Study # ID-078-114, tablet formulation). No significant accumulation is expected at steady state with the proposed maximum therapeutic dose (Study # AC-078-102, Part-A; Racc: ~1.07 at 75 mg). A less than dose proportionate increase was observed for daridorexant exposures (Cmax and AUC) at doses above 50 mg potentially due to the limited aqueous solubility (Study # AC-078-101).

The human mass balance evaluation indicates that ~57% of the drug is excreted in feces, and ~28% in urine (Study # AC-078-101). The studies indicate that daridorexant undergoes extensive metabolism (primarily by CYP3A4; ~89%) forming ~77 metabolites (major: M1, M3, and M10) mostly by oxidative transformations (unchanged excreted: total ~0.3%). Concomitant administration of daridorexant with an inhibitor of CYP3A4 is resulted in increased exposures of daridorexant (with moderate inhibitor: Cmax: ~1.4-fold & AUC: ~2.4-fold). Reduced dose (i.e., 25 mg) is recommended during concomitant administration of daridorexant with a moderate inhibitor of CYP3A4. While, concomitant administration of daridorexant with a strong inhibitor of CYP3A4 is not recommended. An increase in the unbound fraction of daridorexant was observed (~2.3-fold) in subjects with moderate hepatic impairment. The sponsor proposed dose reduction (i.e., 25 mg) in subjects with moderate hepatic impairment and the product is not recommended for subjects with severe hepatic impairment (Study # ID-078-112). The sponsor states that the evening administration of daridorexant did not alter PK parameters (25 mg; Study # AC-078-102).

Previously, the sponsor proposed to evaluate QT effects of their product using a thorough QT study using concentration-corrected QT analysis (Study # ID-078-117). This was a randomized, double-blind, placebo- and moxifloxacin-controlled, 4-way crossover study evaluating the effect of single therapeutic (50 mg, tablet) and supratherapeutic (150 mg, tablets) doses of daridorexant on the QT interval duration in healthy subjects (n=30). All study treatments were administered at bedtime at least 4 h after the evening meal of Day 1 of each period. The IRT reviewed the sponsor's QT assessment plan under IND-128789. Although the highest clinically relevant exposure scenario was not identified, the study design and analysis plan were acceptable. Finally, the sponsor conducted study using 200 mg as a supratherapeutic dose. Refer to previous IRT review in DARRTS (link).

3.1.2 Nonclinical Safety Pharmacology Assessments

In cells expressing hERG K^+ channels, daridorexant led to a concentration-dependent reduction of inward and outward K^+ currents with an IC20 of 7.4 μM and an IC50 of 25 μM. At the human dose of 50 mg in AC-078-101 (single-dose administration, Cmax = 1231 ng/mL, in vitro free fraction = 0.3%), this provides a margin of 920 between the free daridorexant concentration in humans and the IC20 on the hERG ion channel. In the dog telemetry study, HR decreased slightly at dose levels of 10, 30, and 100 mg/kg/day. Therefore, ECG intervals PR, RR, and QT were slightly prolonged. QT interval durations corrected for HR (QTc) were unchanged. These findings were considered not adverse, and the no-observed-adverse-effect level was 100 mg/kg. The risk of QT prolongation in humans is considered minimal in light of large safety margins for in vitro hERG channel blockade and absence of effects on the QTc interval in vivo.

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Reviewer's assessment: *The sponsor evaluated the effects of daridorexant on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The GLP hERG study report (link) describes the potential effects of daridorexant on the hERG current in HEK293 cells. The hERG current was assessed at a temperature of 36 ± 1 °C, using a step-step voltage protocol (from a holding potential of -80 mv to a depolarizing pulse of 20 mV for 2 second, followed by a repolarizing pulse to -40 mV for 2 second) that is different from the recommended hERG current protocol by the FDA (link). The reviewer does not expect protocol differences to impact hERG current pharmacology. The positive control (100 nM E-4031) inhibited hERG potassium current by 94.5%. Samples of the test article formulations (nominal concentrations at 60 mM) collected from the stock solution were analyzed for concentration verification. These results were within ± 5.0% of nominal, thereby meeting the acceptance criteria.*

Daridorexant inhibited hERG currents by 9.3 % at 3 μM, 26.9% at 10 μM, 52.4% at 30 μM and 75.4% at 60 μM. The IC50 for the inhibitory effect of daridorexant on hERG potassium current was 25 μM (Hill coefficient = 1.1). The safety margin of daridorexant against (inhibit) hERG is provided below:

Table 1: Safety Margin of Daridorexant on hERG Current

	Cmax (ng/mL)	**Protein Binding**	**Free Cmax** (ng/mL)	**hERG IC50** (μM)	**Mol Weight** (g/mol)	**Safety Margin** (Ratio)
Daridorexant	1308	>99%	13.08	25	450.93	862x

Cmax was 1308 ng/mL with 75 mg QD, at Day 5 (link)

The in vivo study (link) assessed effects of single oral dose of daridorexant up to 100 mg/kg on ECG parameters in dogs. Each animal served as its own control and received the vehicle and 3 doses of the test item for the telemetry recording and one dose of the test item for the toxicokinetic session. A minimum wash-out period of at least 3 days was applied between each dose. Blood for toxicokinetics was sampled before dosing and 1, 2, 3, 5, 7, 10 and 24 hours after dosing on day 40. The mean Cmax were 9310 ng/mL (female dogs) and 8900 ng/mL (male dogs) at 100 mg/kg. The exposure exceeded the therapeutic exposure level in humans (1401 ng/mL). No positive control drug was included in this study. No QTc changes were observed at oral dose up to 100 mg/kg of daridorexant in dogs.

In summary, although in vitro hERG assay showed deviation from the best practice considerations for an in vitro assay according to the new ICH S7B Q&A 2.1 (link) daridorexant has a low risk for QT prolongation by directly inhibiting the hERG channel at therapeutic exposure (hERG safety margin: 862x). Daridorexant at oral dose up to 100 mg/kg didn't prolong QTc in male and female dogs.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for daridorexant was based on exposure-response analysis, please see Section 3.2.3 for additional details.

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In the by-time-point (central tendency) analysis, a linear mixed-effects model for ΔQTcF was developed. The analysis was performed using the ECG set. Fixed effects were included for time point, treatment, period, sequence, interaction between treatment and time point, and centered baseline $QTcF_{OBS}$.

Sponsor's by-time analysis shows no significant increase in QTcF, HR and QRS. A borderline increase observed in PR interval.

Reviewer's comment*: FDA reviewer's analysis used linear mixed-effects model and adjusted for time-matched baseline as a fixed effect. No significant increase observed in QTcF, HR, PR and QRS.*

3.2.1.1 Assay Sensitivity

By-time analysis was the primary analysis for assay sensitivity. Concentrations of moxifloxacin were not determined in the present study. By-time analysis results shows that assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *FDA reviewer's analysis also shows that assay sensitivity was established, and results are similar to the sponsor's results. This drug was administered at nighttime. Thus, the moxifloxacin profile deviated from the normal profile.*

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

Reviewer's comment: *Sponsor's by-time moxifloxacin analysis results deviate from the historic moxifloxacin profile. FDA reviewer performed QT bias analysis and no significant bias was observed.*

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or > 60 msec over baseline, HR (>100 beats/min), and QRS (>120 msec and 25% over baseline). One subject in daridorexant 50 mg dose level and one subject in daridorexant 200 mg dose level experienced PR greater than 220 msec and increase was more than 25% compare to the baseline PR values. Sponsor also reported T-wave abnormality in both dose levels of daridorexant.

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor explored the PK/PD relationship between the change from baseline in QTc interval (ΔQTcF) and the plasma concentration of daridorexant using linear mixed effects model (Garnett et al 2018). The sponsor's analysis shows that there was a slight positive slope of 4.13×10^{-3} msec/ng/mL (p-value 0.55) for the relationship between ΔQTcF and plasma concentration of daridorexant. Based on the linear model the predicted ΔΔQTcF was 1.837 msec (upper 90% CI 3.792 msec) at the mean Cmax of 1809 ng/mL associated with 200 mg dose. The sponsor's analysis indicates an absence of significant QTc prolongation upon oral administration of daridorexant.

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Reviewer's comment: *The conclusion of the reviewer's analysis agreed with the sponsor's analysis. Please see Section 4.5 for details.*

3.2.4 Safety Analysis

AEs were infrequent and reported by 5 out of 36 subjects (daridorexant 50/200 mg: n = 1/2; moxifloxacin: n = 2; placebo: n = 1).

The most frequent AE was headache which was reported in 3 subjects (1 subject after 200 mg daridorexant and 2 subjects after 400 mg moxifloxacin). AEs were of mild or moderate intensity except for 1 AE of headache that was assessed as severe following administration of 400 mg moxifloxacin.

No deaths or other SAEs occurred during the study (from Screening until EOS). After EOS, 1 SAE (hospitalization due to migraine attack) was reported for 1 subject during the safety follow-up period.

One subject discontinued the study treatment after administration of 50 mg daridorexant due to vomiting. This event occurred 5 min after drug administration and lasted for 13 min. It was mild and not suspected to be drug-related, as it was preceded by nausea occurring already prior to dosing. The same subject had previously experienced vomiting after 200 mg daridorexant in this study. No clinically relevant changes in vital signs, body weight, laboratory variables, and ECG parameters were identified during the study.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

QT bias assessment was conducted by evaluating the relationship between the difference between the sponsor provided QT measurements and the automated algorithm used by the ECG Warehouse and the mean of the two measurements (BA-slope). The resulting BA-slope by treatment (active/placebo/overall) is presented for QTcF for daridorexant (Table 2) and moxifloxacin (Table 3). This analysis does not suggest the presence of significant negative treatment bias.

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Table 2: QTcF bias assessment by treatment (Daridorexant)

Treatment	# of ECGs	mean (sd), msec	Slope [95% CI], msec per 100 msec
All	4992	-3.16 (6.39)	-2.66 [-3.38 to -1.94]
Daridorexant	3408	-3.35 (6.37)	-2.41 [-3.27 to -1.54]
Placebo	1584	-2.74 (6.39)	-3.2 [-4.51 to -1.88]

Table 3: QTcF bias assessment by treatment (Moxifloxacin)

Treatment	# of ECGs	mean (sd), msec	Slope [95% CI], msec per 100 msec
All	3249	-2.97 (6.72)	-2.86 [-3.77 to -1.95]
Moxifloxacin	1665	-3.19 (7.01)	-2.5 [-3.78 to -1.22]
Placebo	1584	-2.74 (6.39)	-3.2 [-4.51 to -1.88]

4.3 By-Time Analysis

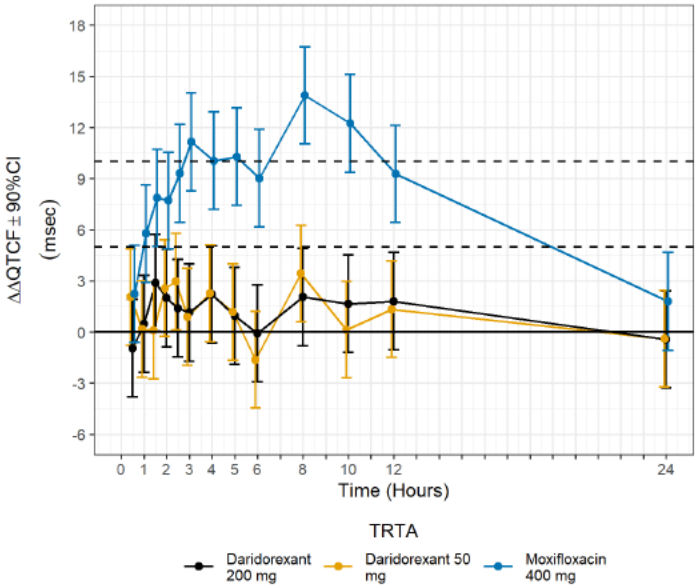
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and compound symmetry covariance matrix to explain the association between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 4.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).



Reference ID: 4808019

Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTcF (msec)	90.0% CI (msec)
Daridorexant 200 mg	35 / 33	1.5	2.9	(0.0 to 5.7)
Daridorexant 50 mg	35 / 33	8.0	3.4	(0.6 to 6.3)

4.3.1.1 Assay sensitivity

Assay sensitivity was assessed using by-time analysis. The statistical reviewer used the same linear mixed model to analyze the moxifloxacin effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The time-course of changes in ΔΔQTcF is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 5).

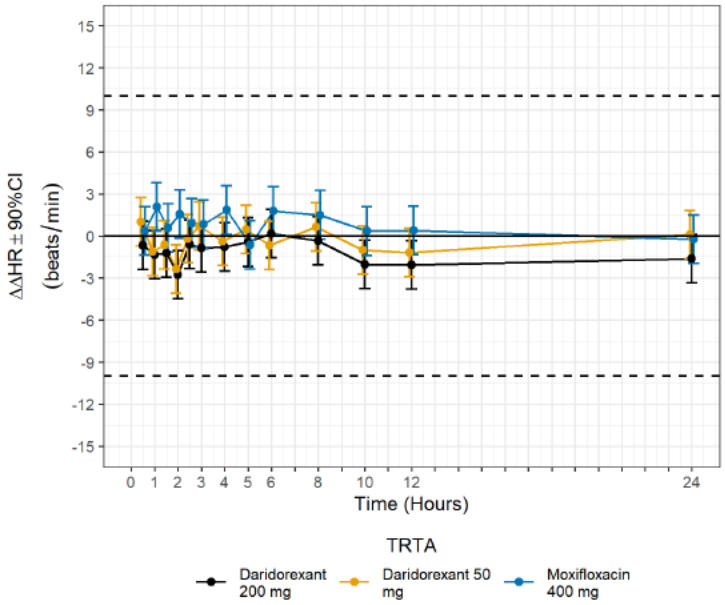
Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTcF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	34 / 33	8.0	13.9	(11.0 to 16.7)	(10.0 to 17.8)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

Figure 2: Mean and 90% CI of ΔΔHR Timecourse

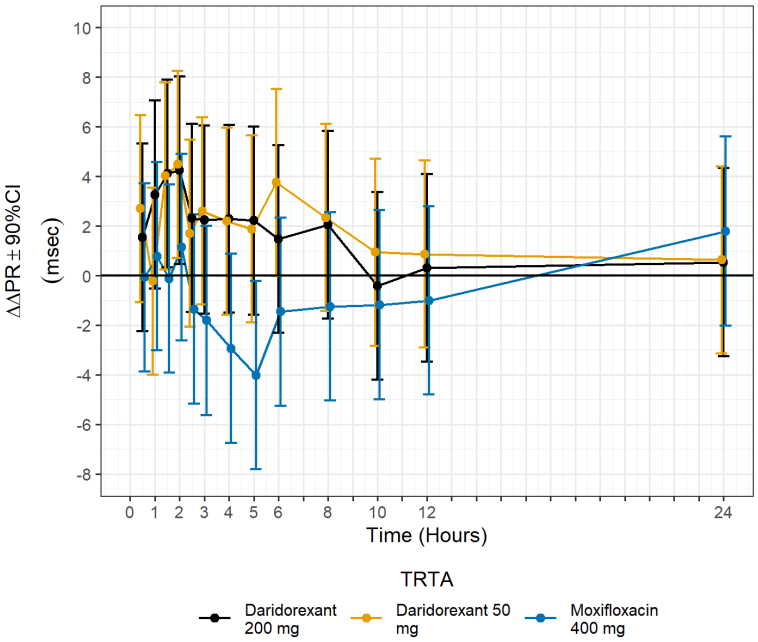


4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

Reference ID: 4808019

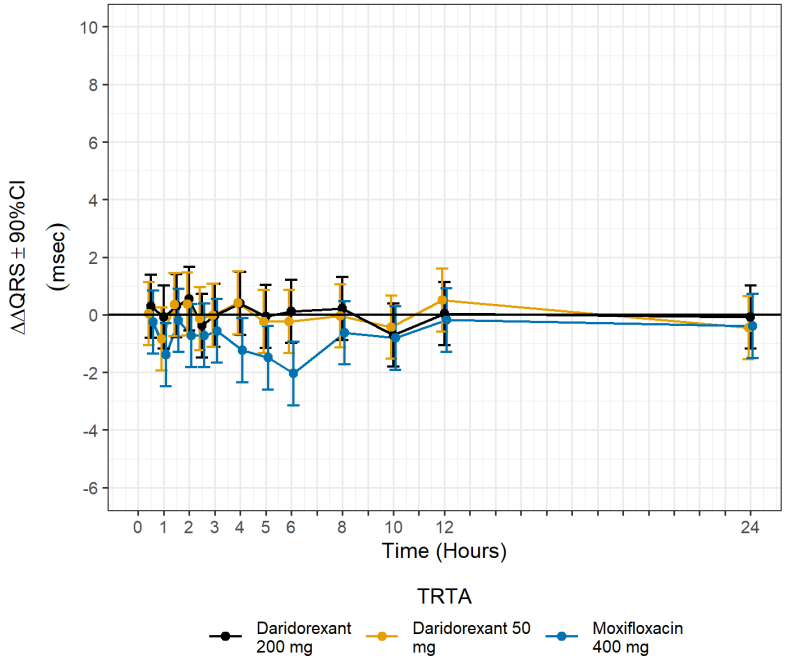
Figure 3: Mean and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse



Reference ID: 4808019

4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcF greater than 480 msec and/or none of the subjects experienced ΔQTcF greater than 60 msec in both dose levels of daridorexant.

4.4.2 HR

None of the subjects experienced HR greater than 100 beats/min in both dose levels of daridorexant.

4.4.3 PR

Table 6 lists the categorical analysis results for PR (less than 200 msec; between 200 and 220 msec and above 220 msec with and without 25% increase over baseline). If a category is omitted that means that no subjects had values in that category. There was one subject in daridorexant 50 mg dose group and one subject in daridorexant 200 mg dose group who experienced PR greater than 220 msec and increase was greater than 25% compare to the baseline PR values.

Table 6: Categorical Analysis for PR

Treatment	Total (N)		Value <= 220 msec		Value > 220 msec & < 25%		Value > 220 msec & >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Daridorexant 50 mg	35	468	33 (94.3%)	451 (96.4%)	1 (2.9%)	14 (3.0%)	1 (2.9%)	3 (0.6%)
Daridorexant 200 mg	35	455	33 (94.3%)	441 (96.9%)	1 (2.9%)	8 (1.8%)	1 (2.9%)	6 (1.3%)
Placebo	33	429	31 (93.9%)	414 (96.5%)	2 (6.1%)	15 (3.5%)	0 (0%)	0 (0%)

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec in both dose levels of daridorexant.

4.5 EXPOSURE-RESPONSE ANALYSIS

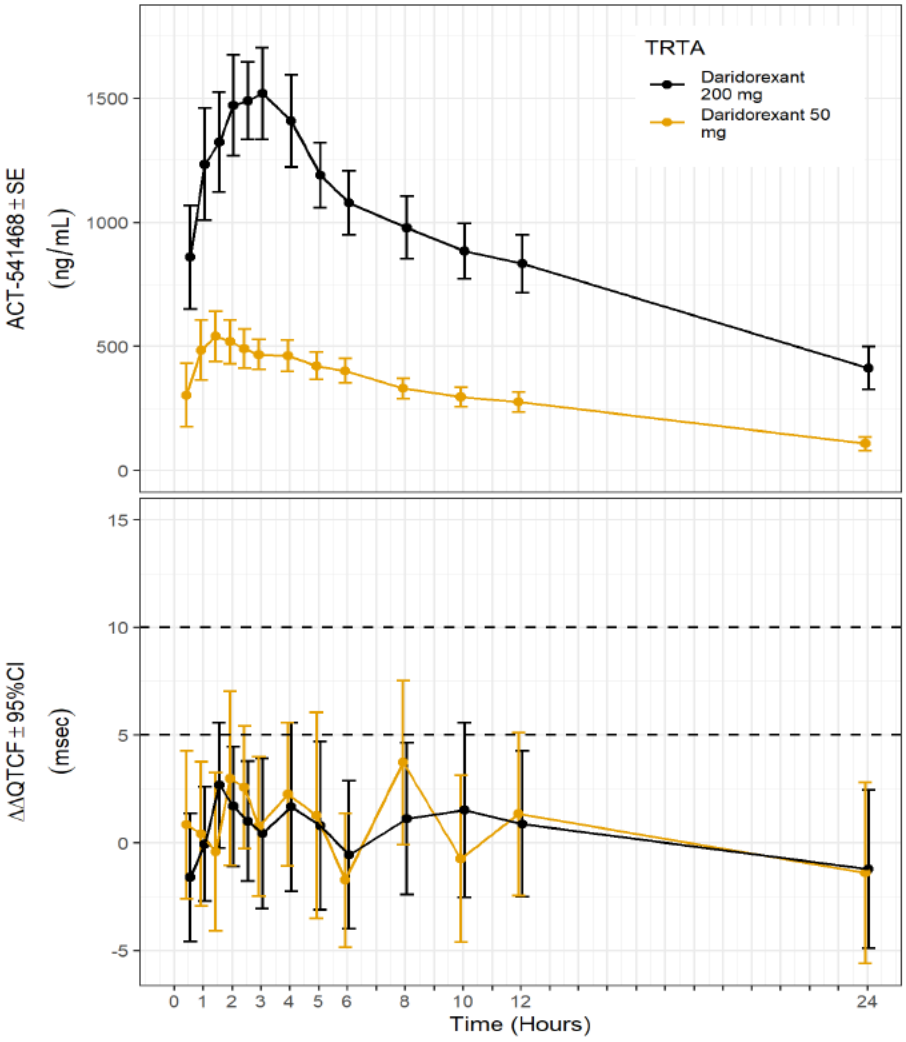
The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of daridorexant and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between daridorexant concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: - 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) absence of significant delay between daridorexant concentration and ΔQTc and 3) absence of significant a non-linear relationship.

Reference ID: 4808019

An evaluation of the time-course of daridorexant concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of daridorexant indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 5 bpm (Sections 4.3.2 and 4.4.2).

Figure 5: Time course of daridorexant concentration (top) and QTc (bottom)

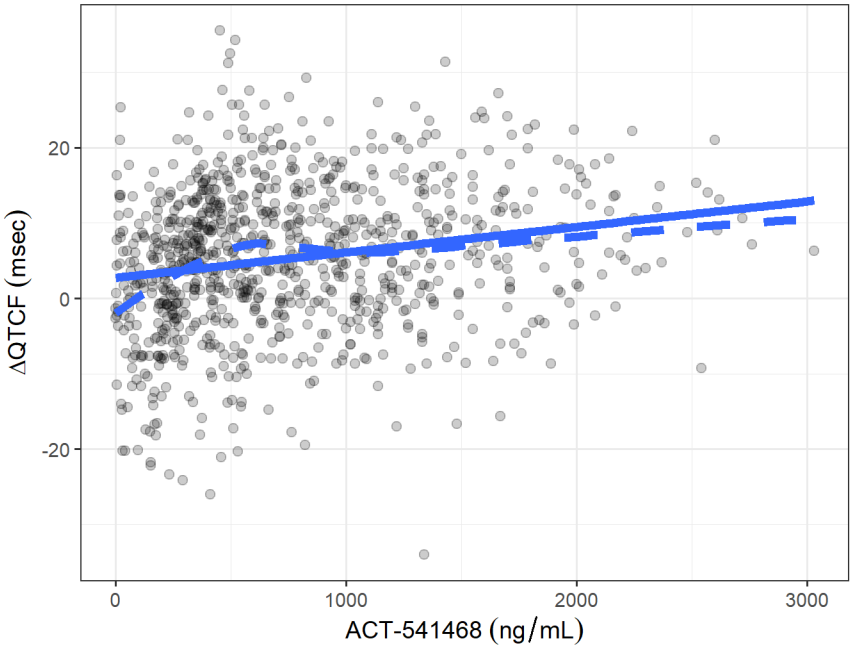


Note: ΔΔQTcF vs. time plot is based on descriptive statistics.

After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between daridorexant concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between daridorexant concentration and ΔQTc and supports the use of a linear model.

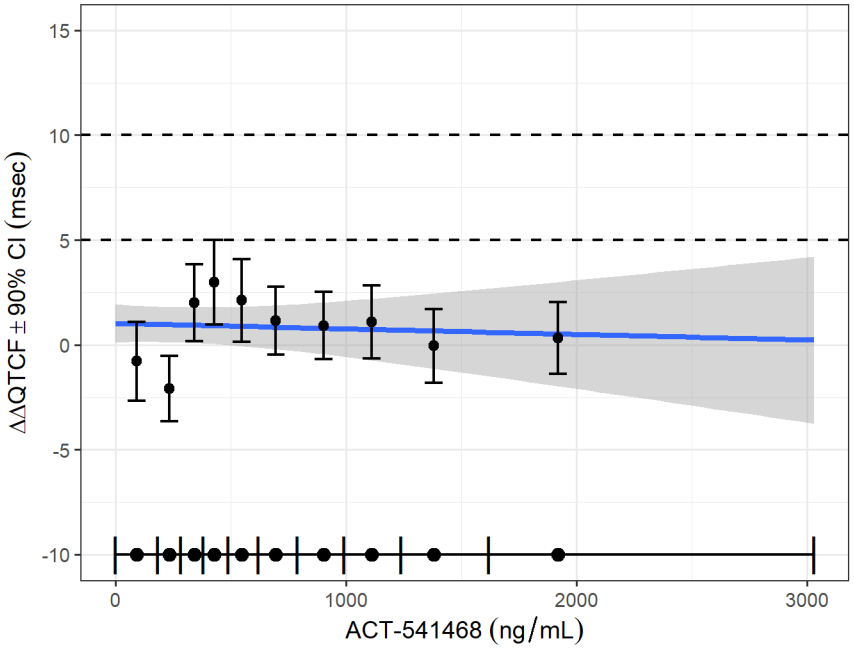
Reference ID: 4808019

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 1.

Figure 7: Goodness-of-fit plot for QTc



4.5.1 Assay sensitivity

Assay sensitivity was established using by time analysis. Please see Section 4.3.1.1 for additional details.

Reference ID: 4808019

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PHARMACOLOGIST REVIEW OF GLP EIR

Firm Name: [redacted] Safety Assessment (SAS)
City, State: [redacted]
Assignment Date: [redacted]
EI Start Date: [redacted]
EI End Date: [redacted]
FDA Participants: NA
The inspection was performed by [redacted]

Inspection Type: Directed
FDA – 483 Issued: No

Inspection Summary

This was a FY2021 directed inspection of [redacted], performed at the request of the CDER OND Division of Psychiatry. The inspection was performed by [redacted] to address the CDER review division's concerns with data quality and integrity of four GLP studies. Eight minor observations were listed in the inspection report. The study data are reliable for Agency review.

Studies Audited during this Inspection

Study No.: T16.017 ([redacted])
Study Title: ACT-541468A: 39-Week Toxicity Study by the Oral (Gavage) Route in the Beagle Dog Followed by an 8-Week Treatment-Free Period
Study Initiation Date: 6/20/2016
Final Report Date: 3/27/2018
Study Director: [redacted]

Study No.: T15.076 ([redacted])
Study Title: ACT-541468A: 26-Week Oral (Gavage) Toxicity Study in the Rat Followed by an 8-Week Treatment-Free Period
Study Initiation Date: 12/10/2016
Final Report Date: 1/10/2019
Study Director: [redacted]

Study No.: T19.005 ([redacted])
Study Title: Pre- and Postnatal Development Study of ACT-541468A by the Oral (Gavage) Route in the Rat (Segment III)
Study Initiation Date: 4/18/2019
Final Report Date: 7/7/2020
Study Director: [redacted]

Study No.: T16.060 ([redacted])
Study Title: ACT-541468A: 104-Week Carcinogenicity Study by the Oral (Gavage) Route in the Rat
Study Initiation Date: 5/4/2017

Final Report Date: 8/30/2020
Study Director: [redacted]

IND No.: 128789 (NDA 214985)
Review Division: ON/DP
Sponsor: Idorsia Pharmaceuticals, Ltd., Cherry Hill, NJ

Background:
[redacted] is a contract research organization (CRO) performing nonclinical studies. The name of the facility has changed many times including [redacted] Currently the facility has [redacted] employees and [redacted] of them are working on GLP studies. About [redacted] nonclinical studies are performed each year and about 65-70% of the studies are conducted in compliance with OECD Principles of GLP.

Prior Inspection:
The facility is regularly [redacted]) inspected by [redacted]
There have been no US FDA GLP inspections performed at the site.

Current Inspection:
Studies audited during the current inspection are listed above. In addition to data auditing, the following areas were covered by interviewing study personnel and by checking study data: QAU, staff training, study conduct, equipment, test and control articles, SOPs, animal care and archives.

OND concerns with animal handling and treatment
The inspector compared all relevant events across the studies to detect a common parameter among them (e.g., dates, personnel, links between incidents). The results are summarized below.

General: The study personnel involved in the events were all different, indicating the lack of training or skills is not the cause of the study issues.

[redacted]

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Reference ID: 4801442

(b) (4)

OSIS Evaluation: The inspector investigated and verified animal care and dosing error concerns identified by the CDER reviewer. For dosing errors (b) (4)), no TK samples were affected. In addition, as this was a two-year carcinogenicity study, the missing doses (b) (4) may not present a significant impact on the quality and integrity of the study data. The study directors accurately reported the mortality due to gavage errors, head injury, and unknown reasons in the study reports, so the data should be reliable for FDA's review. Other items including animals in the wrong cage and outside the cage are unlikely to significantly impact data quality and integrity of the audited studies because of the low incidence. However, these animals should be excluded from the study as there is no way to know what happened to these animals while they were out of the cage or female animals were put into the male animal cage.

Observations: At the conclusion of the inspection, eight minor observations were discussed with the firm's management. No response from the firm was provided. The observations and OSIS'

evaluation follow.

(b) (4)

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(b) (4)

Recommendations:

- Issues related to animal care, welfare and dosing errors in the four audited studies were investigated by the (b) (4) inspector and confirmed to be isolated cases.
- The data from the four audited studies are reliable.

cc: via DARRTS Click or tap here to enter text.
OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza/Johnson
CDER-OSIS-GLP@fda.hhs.gov
OSIS/DNDSI/Bonapace
cc list ORA/Eric Pittman
OND/ON/DP and DPT-N/Jia Yao, Wilson Latrice, Aisar H. Atrakchi (NDA 214985 and IND 128789) Choose an item. Choose an item.
Draft: (ZC 5/18/2021)
Edits: (LLL 5/18/2021; CB 5/20/2020)
ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/GLP Program/(b) (4) Post-Inspection Folder/EIR & EIR Review
OSIS File #: NA
FACTS: NA
FEI: NA

Reference ID: 4801442

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05/25/2021 08:00:37 PM

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